2018 Studies in social security and health | 150

Hanna Koskinen

Pharmaceutical expenditures, the reference price system and competition in the pharmaceutical market

A register study

Studies in social security and health 150 | 2018

Hanna Koskinen

Pharmaceutical expenditures, the reference price system and competition in the pharmaceutical market

A register study

To Kukka

Author

Hanna Koskinen, MHS (Health Economics), researcher
Kela Research, the Social Insurance Institution of Finland
firstname.lastname@kela.fi

The publications in this series have undergone a formal referee process.

Layout: Pekka Loiri

ISBN 978-952-284-039-4 (print)
ISBN 978-952-284-040-0 (pdf)

ISSN-L 1238-5050
ISSN 1238-5050 (print)
ISSN 2323-7724 (pdf)

URI http://urn.fi/URN:NBN:fi-fe2018052524702

Publisher: Kela, Helsinki, 2018

Printed by Erweko

Painotuot
4041 003

ECOFILM

Abstract

Koskinen H. **Pharmaceutical expenditures, the reference price system and competition in the pharmaceutical market. A register study.** Helsinki: The Social Insurance Institution of Finland, Studies in social security and health 150, 2018. 132 pp. ISBN 978-952-284-039-4 (print), 978-952-284-040-0 (pdf).

This study examines the impact of the implementation of a generic reference price system on pharmaceutical prices and competition within the market. The focus is particularly on antipsychotic medications. Furthermore, the impact of reference pricing on previously implemented generic substitution is assessed. Antipsychotics and antidepressants were, in terms of value, among the fastest growing pharmaceutical groups in Finland at the turn of the 21st century. For antipsychotics, most of the cost growth resulted from the rise in the mean daily cost of treatment, whereas the main reason for antidepressant cost growth was the increased number of patients. The implementation of reference pricing decreased the daily cost of the studied antipsychotics. The decreases ranged from 30% to 66% in the short term and from 25% to 51% in the medium-to-long term. When the study was extended to other pharmaceutical groups, the average decrease was 35% at the end of the first year, 56% at the end of the second year and 60% at the end of the third year. However, there were large differences in the size of the decrease between groups. Being included in the reference price system had the largest decreasing impact on prices. However, the reference price system's impact on prices appeared to be waning; the later an active substance was included in the system, the higher the price level remained. In addition, the impact of the reference price system on previously implemented generic substitution remained low, and 2.5 years after the implementation of the reference price system it was almost non-existent. Generic pharmaceutical markets are highly concentrated in Finland. In addition, there is an overall lack of transparency in the pharmaceutical distribution chain. Further research is needed on the barriers of entry and on the role different operators of the pharmaceutical distribution chain have in promoting price competition in the generic market sector.

Keywords: reference prices; systems; generic substitution; prices; competition; drugs, generic; generic products; medicines; antipsychotic agents; market; costs

Tiivistelmä

Koskinen H. **Lääkekustannukset, viitehintajärjestelmä ja kilpailu lääkemarkkinoilla. Rekisteritutkimus.** Helsinki: Kela, Sosiaali- ja terveysturvan tutkimuksia 150, 2018. 132 s. ISBN 978-952-284-039-4 (nid.), 978-952-284-040-0 (pdf).

Tutkimuksessa tarkastellaan geneerisen viitehintajärjestelmän käyttöönoton vaikutusta lääkkeiden hintoihin ja markkinoilla esiintyvään kilpailuun. Lisäksi arvioidaan viitehintajärjestelmän tuomaa lisähyötyä suhteessa aikaisemmin käyttöönotettuun lääkevaihtoon. Erityisesti tarkastellaan psykoosilääkkeitä, jotka olivat 2000-luvun vaihteessa masennuslääkkeiden tapaan kustannuksissa mitaten eräs nopeimmin kasvavista lääkeryhmistä Suomessa. Suurin osa psykoosilääkkeiden kustannusten kasvusta johtui keskimääräisen hoitopäiväkustannuksen noususta. Masennuslääkkeiden kustannuskasvua taas selitti lisääntynyt potilaiden määrä. Viitehintajärjestelmän käyttöönotto pienensi psykoosilääkkeiden hoitopäivän kustannusta lyhyellä aikavälillä 30–66 prosenttia ja pidemmällä aikavälillä 25–51 prosenttia. Kun tarkastelua laajennettiin muihin lääkeryhmiin, oli keskimääräinen lasku vuoden päästä 35 prosenttia, kahden vuoden päästä 56 prosenttia ja kolmen vuoden päästä 60 prosenttia. Lääkeryhmien välillä oli kuitenkin suuria eroja. Itse viitehintajärjestelmään liittämisellä oli merkittävin vaikutus sen piiriin kuuluvien valmisteiden hintoihin. Järjestelmän kyky vaikuttaa hintoihin näytti kuitenkin hiipuvan: mitä myöhemmin lääkeaine liitettiin järjestelmään, sitä korkeampana sen hintataso pysyi. Lisäksi viitehintajärjestelmän tuoma lisähyöty suhteessa aikaisemmin käyttöönotettuun lääkevaihtoon oli vähäinen. 2,5 vuotta viitehintajärjestelmän käyttöönoton jälkeen lisähyöty oli lähes olematon. Geneeriset lääkemarkkinat ovat Suomessa erittäin keskittyneet, ja lääkkeiden jakeluketjun läpinäkyvyydessä on puutteita. Markkinoille pääsyn esteet ja jakeluketjun eri toimijoiden roolit kilpailun edistämisessä vaativat vielä lisää tutkimusta.

Avainsanat: viitehinnat; järjestelmät; lääkevaihto; hinnat; kilpailu; geneeriset lääkkeet; rinnakkaisvalmisteet; lääkkeet; psykoosilääkkeet; markkinat; kustannukset

Sammandrag

Koskinen H. **Läkemedelskostnader, referensprissystemet och konkurrens på läkemedelsmarknaden. En registerstudie.** Helsingfors: FPA, Social trygghet och hälsa, undersökningar 150, 2018. 132 s. ISBN 978-952-284-039-4 (hft.), 978-952-284-040-0 (pdf).

I denna studie undersöktes effekten av införandet av det generiska referensprissystemet på läkemedelspriserna och konkurrensen på marknaden med särskild inriktning på antipsykotiska läkemedel. Vidare utvärderades den positiva effekten av referensprissättning på den tidigare implementerade generisk substitutionen. Antipsykotiska och antidepressiva läkemedel hörde till de snabbast växande läkemedelsgrupperna i Finland i början av 2000-talet. I fråga om antipsykotiska läkemedel berodde största delen av kostnadsökningen på att den genomsnittliga kostnaden för en vårddag steg. I fråga om antidepressiva läkemedel var orsaken till kostnadsökningen att antalet patienter ökade. Införandet av referensprissystemet minskade den dagliga kostnaden för antipsykotiska läkemedel med mellan 30 % och 66 % på kort sikt och med mellan 25 % och 51 % på medellång till lång sikt. När studien utvidgades till andra läkemedelsgrupper var den genomsnittliga minskningen 35 % vid slutet av det första året, 56 % vid slutet av det andra året och 60 % vid slutet av det tredje året. Det fanns dock stora skillnader i storleken på minskningen mellan olika läkemedelsgrupper. Den faktiska upptagningen i referensprissystemet hade den största minskande effekten på priserna. Referensprissystemets inverkan på priserna var dock avtagande. Ju senare en aktiv substans ingick i referensprissystemet, desto högre förblev prisnivån. Dessutom var den positiva effekten av referensprissystemet jämfört med den tidigare implementerade generiska substitutionen låg. Två och ett halvt år efter att ett läkemedel upptagits i referensprissystemet var effekten nästan obefintligt. De generiska läkemedelsmarknaderna i Finland är starkt koncentrerade. Dessutom finns det en övergripande brist på transparens i läkemedelsdistributionskedjan. Ytterligare forskning behövs om inträdesbarriärer och olika aktörers roll i distributionskedjan.

Nyckelord: referenspriser; system; läkemedelsutbyte; priser; konkurrens; generiska läkemedel; synonympreparat; läkemedel; antipsykosmedel; marknaden; kostnader

Acknowledgements

This study was carried out at Kela, the Social Insurance Institution of Finland. I am very grateful for the opportunity of working at Kela while also working on this thesis.

I want to express my gratitude to my supervisors, Docent Jaana Martikainen and Research Professor Hennamari Mikkola for all their support, encouragement and advice throughout this process. Jaana, you have the exceptional ability to see what is essential and never lose sight of that. Hennamari, you have the rare talent of innovating, developing and thinking outside the box. I wish to thank you both warmly for sharing your wisdom, expertise and insight with me.

I want to sincerely thank my pre-examiners, Professor Janne Martikainen and Dr Christine Leopold, for their invaluable and constructive feedback to the summary. I also wish to thank Professor C. Alan Lyles for accepting the invitation to be my opponent at the public examination of this thesis.

I want to thank my co-authors of the original publications – Jaana Martikainen, Hennamari Mikkola, Leena Saastamoinen, Timo Maljanen and Elina Ahola – for their contribution and enjoyable collaboration. I wish to extend these thanks to all my co-workers at Kela Research and especially to the whole pharmaceutical team. It is difficult to think of a more supportive and generous group of people to work with. I also want to thank my friend and former colleague Ulla Tuominen for the times you have listened to and encouraged me. Further, I want to thank Jaana Ahlstedt and Leena Rautjärvi in Kela publication services for editing the final version of this thesis. I am grateful to have my thesis published in the Studies in Social Security and Health series.

Finally, my deepest gratitude is to my family and loved ones. It is your love and support that enabled me to take this journey.

Helsinki, April 2018

Hanna Koskinen

Contents

List of original publications

This thesis is based on the following original publications:

I **Koskinen H, Martikainen JE, Maljanen T.** Antipsychotics and antidepressants. An analysis of cost growth in Finland from 1999 to 2005. Clinical Therapeutics 2009; 31: 1469–1477.

II **Koskinen H, Ahola E, Saastamoinen LK, Mikkola H, Martikainen JE.** The impact of reference pricing and extension of generic substitution on the daily cost of antipsychotic medication in Finland. Health Economics Review 2014; 4: 9.

III **Koskinen H, Mikkola H, Saastamoinen LK, Ahola E, Martikainen JE.** Time series analysis on the impact of generic substitution and reference pricing on antipsychotic costs in Finland. Value in Health 2015; 18: 1105–1112.

IV **Koskinen H, Martikainen JE, Mikkola H.** Pharmaceutical prices, market structure and competition in reference price system. Empirical evidence from a three-year follow up study. (Submitted)

The publications are referred to in the text by their Roman numerals and reprinted (print edition) by permission of the copyright holders.

List of figures

List of tables

Terms and abbreviations

Active substance	An ingredient that alone or in combination with one or more other ingredients is considered to be responsible for the therapeutic effect of a medicine (WHO Collaborating Centre for Pricing and Reimbursement Policies 2016).
ATC	The Anatomical Therapeutic Chemical classification. A classification system where the active substances are divided into different groups according to the organ or system on which they act and their therapeutic, chemical and pharmacological properties. (The WHO Collaborating Centre for Drug Statistics Methodology 2018.)
DDD	Defined daily dose. The assumed average maintenance dose per day for a drug used for its main indication in adults. (WHO Collaborating Centre for Drug Statistics Methodology 2018.)
EFPIA	The European Federation of Pharmaceutical Industries and Associations
EMA	The European Medicines Agency
EU	The European Union
Fimea	The Finnish Medicines Agency (formerly: the National Agency for Medicines)
Generic medicine	A pharmaceutical product with the same qualitative and quantitative composition in an active substance and the same form as the reference medicine, and whose bioequivalence with the reference medicine has been demonstrated (WHO Collaborating Centre for Pricing and Reimbursement Policies 2016).
GRP	Generic reference pricing. A reimbursement policy in which products containing the same active ingredient are clustered into a reference group. The third party payer funds at maximum to the reference price, while the patient must pay the difference between the purchasing price and the reference price, in addition to any co-payments. (WHO Collaborating Centre for Pricing and Reimbursement Policies 2016.)
GS	Generic substitution. The practice of substituting a medicine with a less expensive medicine containing the same active ingredient/-s. Generic substitution is either allowed or required. (WHO Collaborating Centre for Pricing and Reimbursement Policies 2016.)
HHI	The Herfindahl-Hirschman Index. A statistical measure of market concentration and competition among market participants. It is calculated by summing the squares of the percentage market shares held by the market participants. Also known as the Herfindahl Index. (US Department of Justice 2015.)
Kela	The Social Insurance Institution of Finland

MAH	Marketing authorization holder. Holds the authorization to place and keep a medicine on the market. (WHO Collaborating Centre for Pricing and Reimbursement Policies 2016.)
NHI	The National Health Insurance
Originator medicine	The first version of a medicine. Developed and patented by an originator pharmaceutical company, which has exclusive rights to market the product for the duration of the patent or other exclusivity rights. Often also referred to as brand medicines. (WHO Collaborating Centre for Pricing and Reimbursement Policies 2016.)
Pharmaceutical group	Grouping of active substances according to the organ or system on which they act, and according to their chemical, pharmacological and therapeutic properties. (WHO Collaborating Centre for Drug Statistics Methodology 2018.)
Reference price	A reimbursement ceiling, or the price up to which a third party payer is willing to pay reimbursement for. (WHO Collaborating Centre for Pricing and Reimbursement Policies 2016.)
RPS	A reference price system. A reimbursement policy in which identical medicines or similar medicines are clustered into reference groups. The third party payer funds at maximum to the reference price, while the patient must pay the difference between the purchasing price and the reference price, in addition to any co-payments. (WHO Collaborating Centre for Pricing and Reimbursement Policies 2016.)
TRP	Therapeutic reference pricing. A reimbursement policy in which chemically related, pharmacologically equivalent products or products with similar therapeutic effect are clustered into reference groups. The third party payer funds at maximum to the reference price, while the patient must pay the difference between the purchasing price and the reference price, in addition to any co-payments. (WHO Collaborating Centre for Pricing and Reimbursement Policies 2016.)

1 Introduction

According to Adam Smith, the father of modern economics, the invisible hand of the competitive market results in more benefits to a society than any markets with government-regulated prices could hope for (Smith 1776). However, as pharmaceutical markets demonstrate a high number of market distortions, price competition within the market is inefficient and many governments have felt the need to step in and regulate pharmaceutical prices in one way or another (Rice 1998; Mossialos et al. 2004; WHO 2012).

One example of pharmaceutical price regulation is reference pricing. In a reference price system, third party payers set a reimbursement threshold for a group of products regarded as interchangeable. The purpose is to promote competition between pharmaceutical companies and to encourage consumers to make rational decisions. In a reference price system, regulators attempt to mimic competitive markets by creating incentives for physicians and patients to be price sensitive. This, in return, presumably encourages price competition between pharmaceutical companies. However, it has been debated whether pharmaceutical price regulation, such as reference pricing, actually hinders competition within the market (Garattini and Tediosi 2000; Danzon and Chao 2000; Danzon and Ketcham 2004). Some argue that reference pricing does not provide much incentive for generic manufacturers to price their products or for pharmacists to sell generic pharmaceuticals below the reference price. This may reduce price competition in the end. (Anis et al. 2003; Miraldo 2009.) On the other hand, it has been suggested that countries with less strict price regulation have higher prices than countries with strict price regulation (Kanavos et al. 2008).

Typically, reference pricing is applied to off-patent markets. After an originator product's patent expires, generic products can enter the market and start to compete for a share. The diffusion of generic products and price reductions are interlocked; markets with a high share of generics typically show larger decreases in prices than markets with a low share of generics (Dylst and Simoens 2011). It is often difficult to predict generic entry after the loss of exclusivity rights. There is some evidence that companies tend to enter markets with supply and demand characteristics similar to the company's existing pharmaceuticals, and to markets where they have prior expertise in either distribution or manufacturing. There is also evidence that larger market areas and markets with more hospital sales and products that treat chronic conditions attract more entry. (Scott Morton 1999.)

At the end of the first decade of the 21st century, Finland was facing financial hardship and there was a need to contain public spending. Primarily taxation-financed reimbursement expenditures also came under scrutiny. The increased demand for health care, including pharmaceuticals, the aging population and the adoption of new, often expensive pharmaceuticals all contributed to rising pharmaceutical expenditures. While some measures, including the implementation of generic substitu-

tion in 2003, were already taken, a need for further cost containment existed. (Government proposal 100/2008.) This lead to Finland adopting a generic reference price system in April 2009.

The purpose of this study is to analyse the impact of a reference price system on prices and competition within the market. A special focus is on antipsychotics, which were one of the pharmaceutical groups where outpatient expenditures were growing particularly fast before the implementation of the reference price system. In Chapters 2 and 3, the pharmaceutical sector, rising pharmaceutical expenditures and cost containment are discussed. Chapter 4 introduces the reimbursement and pricing system in Finland, together with the reference price system. Chapter 5 provides a discussion on the competitive conditions of the generic pharmaceutical market in Finland. This is followed by a review of previous literature on the impact of a reference price system on prices (Chapter 6). In Chapters 7 and 8, the rationale and the aims of this study are introduced. An introduction to materials and methods follow in Chapter 9, results in Chapter 10, and lastly a discussion and conclusions in Chapters 11 and 12.

2 The pharmaceutical sector

2.1 The pharmaceutical industry and pharmaceutical product timeline

Between 2011 and 2015, the average growth rate of the global pharmaceuticals markets was 6.2% (IMS Health 2015). North America dominates the market with about 49% of the market in 2016, followed by Europe, which accounts for about 22% of the market. In the European Union (EU), five countries (France, Germany, Italy, Spain and the United Kingdom) account for 68% of the total EU market. (EFPIA 2017.)

In the international perspective, the Finnish pharmaceutical market is rather small, accounting for approximately 1% of the European market (EFPIA 2017). In 2016, the total pharmaceutical sales in Finland were 3,067 million euros, which was 3.7% more than in the previous year. Prescription medicines in outpatient care accounted for 2,137 million euros and over the counter medicines for 352 million euros in retail prices (incl. value added tax, VAT). The rest, 578 million euros in wholesale prices, resulted from sales to hospitals. (Fimea and Kela 2017b.)

According to estimates from the late 2000s, the global pharmaceutical industry is highly fragmented and it consists of thousands of companies of various sizes. Several hundreds of them are research-based companies that have brought at least one new pharmaceutical to the market. (Kyle 2007; OECD 2008.) However, a handful of large international companies control a significant share of the market. (WHO 2005.)

The pharmaceutical industry is one of the most research-intensive industries in the world. According to the OECD, the industry spent about 10–15% of its revenues on research and development in 2011.[1] (OECD 2015.) In Finland, pharmaceutical research and development activity is limited and the number of ongoing clinical trials conducted in Finland has fallen in the 21st century (Fimea and Kela 2017a).

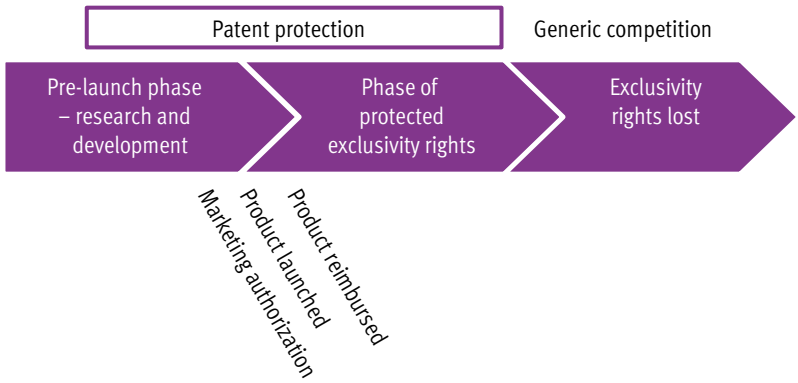
In order to encourage innovation, governments grant intellectual property rights, or patents, to inventors of new products. Patents exclude others from making and selling the invention for the term of the patent. This creates a monopoly position, which allows the pharmaceutical company to recoup its investment, make a reasonable profit and reinvest in research and development. (European Commission 2018.)

The development of a new pharmaceutical product is highly research intensive and time-consuming. The timeline for a new pharmaceutical product divides into three phases: 1) the pre-launch phase where research and development take place, and which ends at the product gaining marketing authorization; 2) the marketing and sales phase during which the product is protected by exclusivity rights; 3) the phase

1 According to the World Health Organization's estimate from 2005, pharmaceutical companies spend one third of all sales revenue on marketing their products. This is roughly twice as much as on research and development. (WHO 2005.)

after exclusivity rights have been lost and generic competition begins. (Figure 1.) The time preceding marketing authorization varies typically between two and ten years, the average being about five years. As companies generally apply for a patent at the beginning of the research and development phase, the effective patent period after the product has received approval is typically much shorter than the term of the patent. The term of the patent is generally 20 years, but supplementary protection certificates, which extend the period of protected exclusivity rights, are often applied. (European Commission 2013.)

Figure 1. Pharmaceutical product timeline.



Like all health care services, pharmaceuticals are typically regarded as merit goods. This encompasses the societal belief that health needs – not individual preferences or the ability to pay – should determine the use of pharmaceuticals. (Fiorito and Kollintzas 2004; WHO 2012.) While European law (EU Directive 2001/83/EC) regulates the marketing authorization of a pharmaceutical product in Europe, national laws regulate pricing and reimbursement systems. In order to promote affordable access to pharmaceuticals, most European countries subsidize the cost of medicine in part or in full for some or all of their population. The scope of the coverage schemes varies between countries. (OECD 2008.) In addition, most European countries have adopted some form of price regulation for reimbursed pharmaceuticals. The aim in regulating prices is both to secure patient access to effective and safe pharmaceuticals and to control expenditures. The used pricing systems often vary between on-patent and off-patent products. (Dukes et al. 2003; Mrazek and Mossialos 2004.)

2.2 The off-patent pharmaceutical market

There are predominantly two types of pharmaceuticals: originator products and generic products. An originator product is the first version of a medicine, developed and patented by an originator pharmaceutical company (WHO Collaborating Centre for Pricing and Reimbursement Policies 2016). A generic product is chemically equivalent and bioequivalent to the originator product but it can only enter the mar-

ket after the patent or other exclusive rights of the originator product have expired. While the originator product must go through an expensive and lengthy research and development process in order to gain marketing authorization, a generic product can enter the market once it has a proven chemical equivalence and bioequivalence to the originator product. This comparatively fast and inexpensive development process allows selling generic products for an often substantially cheaper price. (Baumgärtel 2012; European Medicines Agency 2012.)[2]

Typically, there is a time gap between the loss of exclusivity rights and generic entry. In EU countries, the average time to generic entry was 12.9 months for expiries between 2000 and 2006. For high value products, the time gap was shorter, 7.9 months on average. (Glowicka et al. 2009.)

Generic medicines can play a significant role in securing patient access to affordable pharmaceuticals and reducing pharmaceutical costs. In 2014, the average market share of generic medicines in EU countries was 52% in volume and 24% in value, though there were large differences between countries. In volume, the shares ranged from 9% to 84% and in value from 5% to 41%. In Finland, generics accounted for 40% in volume and 17% in value of the total pharmaceutical market in 2014. This was below the EU average in terms of both volume and value. (OECD 2016b.) The same variation between countries exists in prices. Even 16-fold differences between the highest and the lowest prices of some individual generic products have been observed among EU member states (Kanavos et al. 2011). While the pharmaceutical market and the determinants of pharmaceutical prices are complex, the differences are largely attributable to different regulatory systems and taken cost containment measures (Kanavos et al. 2011; Panteli et al. 2016).

2 The cost of bringing a new pharmaceutical into the market is highly debated. One estimation has been given by the European Federation of Pharmaceutical Industries and Associations (EFPIA), which estimated the development of a new prescription pharmaceutical that gains market approval to cost the pharmaceutical company up to €1,172 million (EFPIA 2015).

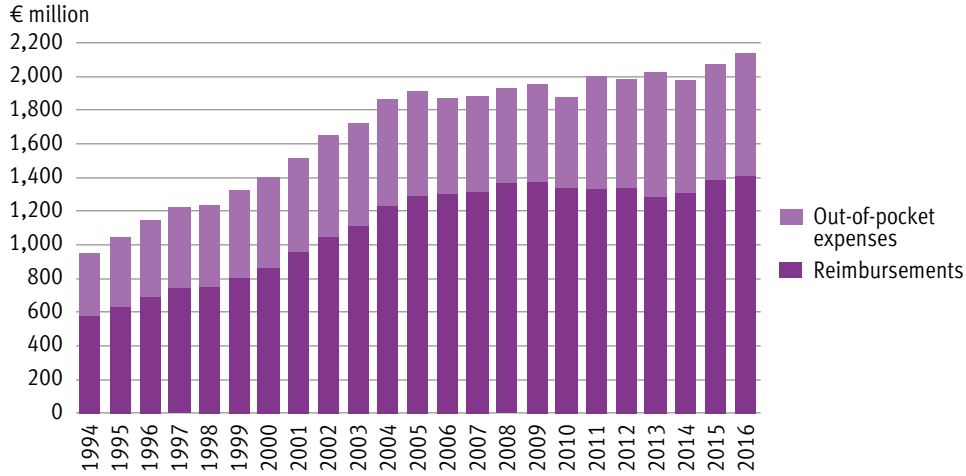
3 Rising expenditures and cost containment in the pharmaceutical sector

3.1 Rising pharmaceutical expenditures

In the early 2000s, pharmaceutical expenditures were growing at a rapid pace in most OECD countries. In addition, the average real annual growth in pharmaceutical spending was faster than the average annual health spending. Between 1990 and 2004, the average real annual growth in pharmaceutical spending was more than 5%, compared with health spending where the growth was 4% on average. However, since the mid-2000s pharmaceutical spending has been increasing at a slower pace. On average, the growth has also been slower than the growth in overall health spending. Between 2005 and 2013, the annual average growth in pharmaceutical spending was 0.7% in real terms compared with 2.4% for overall health spending. (Belloni et al. 2016; OECD 2017.)

In Finland, outpatient pharmaceutical costs and reimbursement costs grew rapidly until the turn of the 21st century but this trend slowed down by the end of the 2000s (Figure 2). In 2016, the total cost for reimbursed prescription pharmaceuticals in outpatient care was 2,137 million euros[3] of which paid reimbursements made up 1,412 million euros. Compared to the year 2015, outpatient pharmaceutical costs and reimbursement costs had grown by 3.6% and 2.5%, respectively. (Fimea and Kela 2016.)

Figure 2. Reimbursed pharmaceutical costs[a] in outpatient care in Finland 1994–2016, divided into reimbursement costs and out-of-pocket expenses.



[a] Deflated to 2016 money with the cost of living index.
Source: Fimea and Kela 1994–2016.

3 An initial deductible of €50 per calendar year was introduced in 2016 (Kela 2017c). The total expenditures presented in this study include purchases under the initial deductible.

The growth in pharmaceutical spending is attributed to two main reasons: increased pharmaceutical use and the introduction of new, higher-priced products. The increased pharmaceutical use reflects both changes in the number of patients and the amounts consumed by patients. New medicines have been introduced for conditions where pharmacotherapies did not exist earlier, and the number of concomitant treatments received per patient has increased (Morgan 2005; Serra-Sastre and McGuire 2009; Sorenson et al. 2013; Karampli et al. 2014). Also, the aging of the population is a contributing factor as the elderly are by and large the largest consumers of health care services, including prescription pharmaceuticals (Kildemoes et al. 2006; de Meijer et al. 2013; OECD 2016a). Diagnostic procedures have evolved and in many conditions pharmacotherapies are initiated in earlier stages, possibly with increased dosages and longer treatments. Treatment practices of, for instance, mental disorders and some types of cancer may also have changed by allowing outpatient care in conditions that used to be treated in inpatient care. (Chernew et al. 2001; de Joncheere et al. 2002; Morgan 2005.) While this shifts costs from inpatient care to outpatient care, it can also raise overall costs through pharmacy margins.

A second reason for the high rates of increase in pharmaceutical spending has been the increased use of higher-priced products. New high-priced products penetrate the market replacing older, less-expensive ones. (Gerdtham and Lundin 2004; Morgan 2005; Shireman et al. 2005; LaFleur et al. 2008.) The landscape of new pharmaceutical products entering the market is changing. The focus has shifted from products for common diseases towards rare diseases and specialty medicines. While some of these medicines produce health benefits, they are also very expensive.

3.2 Supply and demand side measures in cost containment

Rising pharmaceutical expenditures have lead governments to balance with containing public expenditures while still ensuring patient access to affordable medicines. Cost containment measures divide roughly into measures aimed at the supply side and measures aimed at the demand side (Table 1, p. 21). Supply side measures can target the manufacturer level, the wholesale level, and the pharmacy level. The measures, such as reimbursement lists (positive and negative lists), profit control, a cost-plus system[4], substitution by pharmacies, and reference price schemes, aim primarily to regulate the prices of pharmaceuticals either directly or indirectly. (Rietveld and Haaijer-Ruskamp 2002; Ess et al. 2003; Mrazek and Mossialos 2004; Aaserud et al. 2006.) International price comparisons may also have a significant role in the process of setting prices. However, international price comparisons typically become less important when a product enters the off-patent market sector and generic competition begins. (Ruggeri and Nolte 2013.) In addition, even in the on-patent market sector managed entry arrangements between manufacturers and payers or providers are in-

4 Cost-plus pricing is a system where the retail prices of medicines are set by taking into account production costs together with allowances for promotional expenses, manufacturers' profit margins, and charges and profit margins in the supply chain (WHO 2015).

creasingly common. They include both financial and performance based agreements, of which financial based agreements are more common. These agreements include various kinds of non-disclosed discounts to list prices, which makes international price comparisons increasingly difficult. (WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies 2016; Pauwels et al. 2017.)

Demand side measures can be aimed at one or several levels of demand; the patient, the physician or the pharmacy. Demand is primarily influenced with financial or educational measures. While patient co-payments are the most common demand side measure, also caps (a maximum number of prescriptions or drugs that are reimbursed), educational and professional interventions and incentives have been used. Educational interventions can be aimed at the general public, patients or physicians. (Ess et al. 2003; Mrazek and Mossialos 2004; Austvoll-Dahlgren et al. 2008.) However, many of the measures can have an effect on both the demand and supply sides. For example, a German study found that pharmaceutical companies decreased their prices as the patients' co-payment increased (Pavcnik 2002).

Table 1. Measures to contain pharmaceutical expenditures.[a]

Supply-side measures	**Demand-side measures**
Pricing	Cost-sharing
Price controls	Caps
Generic substitution	Co-payments
Reference-based pricing	Moving products to over-the-counter status
International price comparisons	Rational prescribing and use
Pharmacoeconomic evaluations	Educational interventions
Cost-plus pricing	Clinical practice guidelines
Managed entry arrangements	Feedback to physicians
Authorization	Advertising restrictions
Reimbursement lists	Budgets
Price freezes and/or cuts	National, regional or physician level
Profit ceilings	

[a] See e.g. Rietveld and Haaijer-Ruskamp (2002).

3.3 Generic substitution and the reference price system

In generic substitution, pharmacies have either the right or the obligation to substitute a prescribed product with a chemically equivalent but less expensive one. Reference-based pricing[5] is a reimbursement mechanism in which a payer sets a ceiling price for pharmaceuticals that belong to the same cluster. The ceiling price, such as the reference price, is the maximum price for which a reimbursement is paid for all products in the same group. The ceiling price is typically based on the lowest or the average price of drugs in that group. Manufacturers are free to set their prices, but if the price exceeds the reference price, the patient pays the difference in full. (Danzon 2001; Puig-Junoy 2005; Galizzi et al. 2011.)

Generic clustering is the narrowest form of clustering. In generic clustering pharmaceuticals are clustered according to the active substance. This is typically referred to as generic reference pricing. In therapeutic reference pricing, pharmaceuticals with chemically-related, pharmacologically equivalent active substances or a similar therapeutic effect are grouped together. (Dylst et al. 2011.)

The reasoning behind reference pricing is to stimulate competition between manufacturers and rational decision-making by patients (Danzon and Ketcham 2004; Brekke et al. 2007). Therefore, while the reference price system as a cost containment measure is aimed especially at the supply side, it also has an impact on the demand side through patient co-payments. As competition in the pharmaceutical market is typically weak, reference pricing is an attempt to mimic competitive markets and set prices to a competitive level (Danzon and Chao 2000). On the other hand, a German study found that pharmaceutical companies try to compensate reduced revenues in the reference price sector by increasing the price level of their non-reference-priced products. These products are typically first-of-its-kind type of products. (Augurzky et al. 2009.)

5 The term reference pricing can refer either to external or internal reference pricing. In external reference pricing, the price of a pharmaceutical product in other countries are used to set or negotiate the price of the product in a given country. (Remuzat et al. 2015.) In this thesis, the term refers to internal reference pricing.

4 Reimbursement, pricing and the reference price system in Finland

4.1 The reimbursement and pricing of pharmaceutical products in Finland

In Finland, prescription drugs used in outpatient care are reimbursed under the National Health Insurance scheme, which covers all permanent residents in Finland. The patient is reimbursed – typically directly at the pharmacy – according to a pharmacy retail price, which consists of the wholesale price, a statutory pharmacy mark-up, value added tax, and the pharmacists' remuneration. No statutory wholesale mark-ups are in place. The pharmacy mark-up, or the retail price, is calculated according to a formula set by the Finnish Government. (Ministry of Social Affairs and Health in collaboration with the WHO 2011.)

In order for an on-patent pharmaceutical product to be included in the reimbursement system, it is required that the Pharmaceuticals Pricing Board, subordinate to the Ministry of Social Affairs and Health, has confirmed the reimbursement status and the reasonable wholesale price. The Pharmaceuticals Pricing Board makes the decisions on the reasonable wholesale price and the reimbursement status simultaneously and they are valid for a fixed term only. (Fimea and Kela 2016.) In evaluating the applied wholesale price, the Pharmaceuticals Pricing Board takes into account, for instance, the treatment cost incurred and the benefits gained from the use of the pharmaceutical, the prices of comparable pharmaceuticals in Finland, the prices of the pharmaceuticals in other European Economic Area countries, the costs of manufacturing, the research and development of the pharmaceuticals and the funds available for reimbursement. The applicant must also present a health economic evaluation. (Act 1224/2004.)

When a product is included in the reference price system, the Pharmaceuticals Pricing Board confirms a maximum wholesale price for the product. For generic products, the maximum wholesale price for the first product must be 50%[6] lower than the original product's price, and the subsequent generic products cannot be priced higher than other generics. The maximum wholesale price of the originator product is the same as before the loss of exclusivity rights. (Pelkonen 2011; Pharmaceuticals Pricing Board 2015.) However, from 2016 onwards, the Pharmaceuticals Pricing Board applies a reduction to the maximum wholesale prices of originator products in the beginning of the fourth reference price period after the establishment of the reference price group. This pertains to cases where the maximum wholesale price of an originator product is higher than the highest confirmed wholesale price for generic products included in the reference price group. In these cases, a new maximum wholesale price is confirmed, which corresponds to the highest maximum wholesale price of a generic product included in the reference price group. (Pharmaceuticals Pricing Board 2016.) The maximum wholesale price is the maximum price for which wholesalers can sell the product to pharmacies in order for the product to be included in the re-

6 Until January 2016, the percentage was 40.

imbursement system. However, after a product is included in the reference price system, the reimbursement is only paid up to the reference price. (Fimea and Kela 2016.)

4.2 Generic substitution and the reference price system in Finland

Finland adopted mandatory generic substitution in April 2003. Since then pharmacies have been obligated to substitute a prescribed medicine with the cheapest or close to the cheapest interchangeable alternative. Substitutable products must contain the same active substance, the same quantity, have the same route of administration, and the package sizes must be comparable. The products must also be bioequivalent and belong to a pharmaceutical group in which substitution is safe. Substitutable products are included in a list of interchangeable medicines. Fimea compiles the list. (Kela 2017a.)

When only generic substitution was in use, both the physician and the patient could veto the substitution without affecting the reimbursement rate of the product. Stronger monetary incentives were introduced when Finland adopted a generic reference price system in April 2009. Medicines priced at or below the reference price are subsidized according to their purchase price. Medicines above the reference price are subsidized only up to the reference price, and the patient is required to pay the excess in total. If the prescribing doctor vetoes the substitution, the purchase price of the dispensed product is the base for the reimbursement. (Fimea and Kela 2016.)

When generic substitution was introduced, the maximum price difference to the least expensive medicine in the substitution group was €2 when the least expensive product was priced under €40 and €3 when the least expensive product was priced €40 or more. As the reference price system was implemented, the price difference to the least expensive product was narrowed down to €1.50 for products priced under €40 and €2.00 for products priced €40 or more. The price difference was cut down to a single value of €0.50 at the beginning of 2017 (Act 1101/2016). These price differences determine both the reference prices for products belonging to the reference price system and price band ceilings for products that belong only to generic substitution. While reference prices and price bands are determined quarterly, companies give price notifications every two weeks. This means that companies can adjust their prices as early as two weeks after the introduction of new reference prices. (Kela 2017a.)

While Fimea decides which medicines are to be included in generic substitution, the Pharmaceuticals Pricing Board specifies the medicines that are covered by the reference price system. The list of products covered by the reference price system is based on Fimea's list of substitutable products. (Kela 2017a.) When the reference price system was introduced, reference price groups were formed if the reference price group contained at least one reimbursable generic product available on the market. This was amended in 2017 so that a reference price group is also formed if the substitution group contains at least one reimbursable parallel-imported or parallel-

distributed product available on the market. These products remain, however, in the sphere of price confirmation until the first generic product enters the reference price group. (Pharmaceuticals Pricing Board 2017.)

Concurrent with the adoption of the reference price system, the range of medicinal products available for generic substitution was also extended. In Finland, it was not possible to grant product patents for medicinal substances before 1995; only so-called analogy process patents were possible. Though products protected by an analogy process patent were initially included in generic substitution, this decision was amended in 2006 when pharmaceuticals protected by an analogy process patent in Finland were excluded from generic substitution. However, when the Finnish government approved the reference price system, it decided that pharmaceuticals protected by an analogy process patent would again be included in the sphere of generic substitution (Act 803/2008). This meant that products protected by an analogy process patent could be included in generic substitution and the reference price system in Finland even while the products were still under patent protection in many other countries (Saastamoinen et al. 2010; OECD 2014).

In Finland, pharmacies are obliged to provide information and guidance to patients on medicine prices. (Act 395/1987.) In January 2016, the obligation to provide information on medicine prices was amended so that pharmacies now have the obligation to inform the patient of the actual cheapest product within a reference group (Government proposal 330/2014).

Details of generic substitution and the reference price system applied in Finland and main amendments to the systems are presented in Table 2 (p. 26).

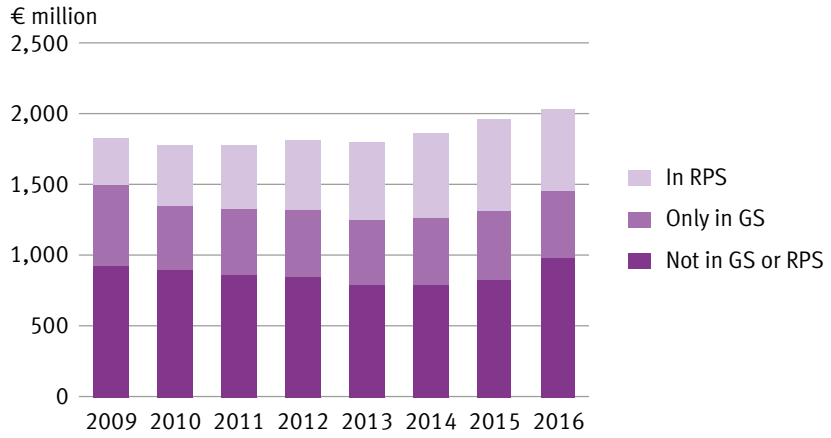
Table 2. Details of generic substitution and the reference price system in Finland and the main amendments to the systems.

	2003	2006	2009	2016	2017
Policies	Generic substitution		Generic substitution and reference pricing		
Grouping	Interchangeable drug list compiled by Fimea: the same active substance in the same amount and pharmaceutical form, biologically equivalent	→ Products protected by analogy process patent excluded	Reference price groups based on Fimea's list of interchangeable drugs if at least one reimbursable generic product in market[a] → Products protected by an analogy process patent included		→ Extension to reference price groups: formed if at least one reimbursable parallel import or distribution product in market
Pricing	All products: free pricing up to maximum wholesale price Generics: at least 40% lower than the originator price		All products: free pricing up to maximum wholesale price Generics: at least 40% lower than the originator price	→ Originator products: maximum wholesale price reviews at the beginning of the fourth reference price period → Generics: at least 50% lower than the originator price	
Price band ceiling / reference price	Least expensive product in the group + €2 (cheapest price under €40) / €3 (cheapest price €40 or more)		Least expensive product in the group + €1.50 (cheapest price under €40) / €2 (cheapest price €40 or more)		→ Least expensive product in the group + €0.50
Price notification	Every 2 weeks Price bands set quarterly		Every 2 weeks Reference prices and price bands set quarterly		
Pharmacies	Mandatory substitution Required to inform patients about prices		Mandatory substitution Required to inform patients about prices	→ Required to inform patients about the least expensive substitutable product	
Physician opposes substitution	Reimbursement based on the dispensed product		Reimbursement based on the dispensed product		
Patient opposes substitution	Reimbursement based on the dispensed product		Reimbursement up to reference price for products incl. in the reference price system		

[a] Some products, for example inhaled corticosteroids, are not included in the reference price system.

In 2016, reimbursed pharmaceuticals belonging to the reference price system accounted for 575 million euros, showing a growth in share from 17.5% in 2009 to 28.3% in 2016 (Figure 3). In the same year, reimbursements for medicine costs were paid to 3.8 million persons of whom 91.7% were reimbursed for at least one product in the reference price system. This share has remained rather stable and it was 88.9% in 2010. At the end of 2016, more than half (56%) of the products in the reimbursement system were included in the reference price system. (Kela 2017b.)

Figure 3. Expenditures of reimbursed pharmaceuticals[a] belonging to the reference price system (RPS), belonging only to generic substitution (GS) or belonging to neither in 2009–2016.

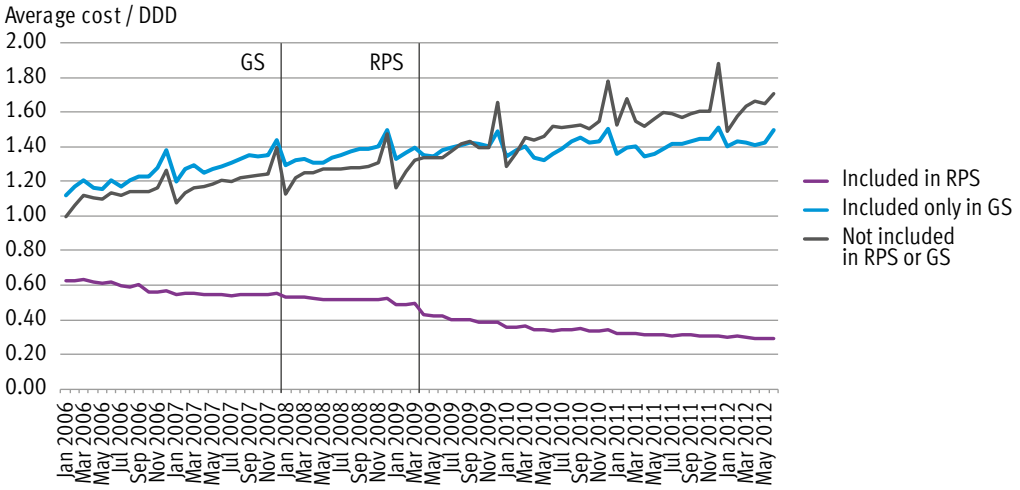


[a] Deflated to 2016 money with the cost of living index.
Source: Kela 2017b.

A Finnish study analysed the impact of implementing the reference price system on the prices of all reimbursed pharmaceutical products. The products were grouped according to whether they were included in the reference price system, included in generic substitution only or not included in either of the systems. Before the implementation of the reference price system, the average daily cost of all included products was €0.63. There was a slight monthly downwards trend preceding the reference price system (–0.4 cents per month) followed by a drop of 4 cents in the level of the average daily cost after the implementation of the system. No statistically significant change was observed in the post-reference price system trend. 39 months after the implementation of the reference price system, the average daily cost of products included in the system was 12.4% lower than it would have been were the reference price system not implemented. However, the implementation of the reference price system also had an impact on the average daily cost of products included only in generic substitution and products not included in either system (Figure 4, p. 28). The impact was the opposite in the two groups. 39 months after the implementation of the reference price system, the average daily cost for products included only in generic substitution was 9.6% lower and for products not included in either system, the

average daily price was 6.3% higher than it would have been were the reference price system not implemented. However, the rising trend in products included in neither system was visible even before the introduction of reference pricing, and the trend escalated only slightly. (Koskinen et al. 2013.)

Figure 4. The average daily cost of products included in the reference price system (RPS), included only in generic substitution (GS) or included in neither system from January 2006 to June 2012.



5 Competition and the pharmaceutical market

In economic theory, perfect competition represents an ideal market structure where competition is at its greatest possible level. Imperfect competition exists when one or more of the conditions for perfect competition are absent. (Begg et al. 2000a.) This chapter reviews the conditions for perfect competition and their presence in the pharmaceutical markets from the buyer's perspective. The conditions are: 1) a large number of buyers and sellers who are all price-takers, 2) homogeneous products, 3) perfect information and 4) free entry and exit to the market. The focus is on competition in the off-patent pharmaceutical market, that is, in situations where the originator product has lost its exclusivity rights and generic products are able to enter the market. More specifically, the focus is on off-patent markets under a reference price system.

A perfectly competitive market requires a set of characteristics to be fulfilled. *Firstly, there should be a large number of buyers and sellers, who are all individually too small to set prices and are thus price-takers*. Supply and demand determine prices. The price determines the buyer's willingness to consume. (Begg et al. 2000b.)

The pharmaceutical industry is a highly research-intensive sector and therefore capital requirements and economies of scale[7] are evident. While capital requirements are less considerable in the off-patent market sector, scale advantages persist. Therefore, large companies are better positioned than small companies to gain and retain market dominance and to influence prices. In addition, incumbency advantages independent of size[8], such as experience from the market and the regulatory system, can give advantage to established companies (Porter 1979). In the last quarter of 2017, there were 972 reference groups included in the Finnish reference price system. Altogether 60 companies gave price notifications for products included in these groups. The companies were of various sizes and some of them have a large selection of products on the market while some have only one or very few. The markets are, however, highly concentrated and according to the OECD, Finland's biggest pharmaceutical company holds a market share of 50%. (OECD 2014.)

Due to insurance, patients typically do not bear the full cost of their pharmaceutical consumption. In situations where patients have low co-payments, there is a risk of overusing pharmaceuticals and low price-consciousness (Scott Morton and Kyle 2012). In addition, physicians seem to be less price-conscious in situations where patients' do not need to bear the full cost of the prescribed pharmaceuticals (Nyman 1999; Danzon and Pauly 2002). A reference price system aims to tackle this issue by placing additional co-payments upon patients if they are unwilling to substitute

7 Economies of scale refers to the competitive advantage large companies have over smaller companies (Silberston 1972).

8 Cost advantage independent of size refers to the advantage entrenched companies may have over newcomers, independent of company size. This advantage can result from e.g. the experience curve, access to materials or a favourable location. (Porter 1979.)

products priced over the reference price with cheaper ones. Therefore, patients are assumed to decrease the consumption of products priced above the reference price and shift the demand to products priced at or below the reference price. (Moreno-Torres 2011.)

In a reference price system, regulators set reference prices for medicines subject to the system. Typically, there is no incentive for patients, physicians or pharmacies to be price-sensitive with prices below the reference price as it has little or no impact on the patient's share of costs and can have a negative impact on pharmacies' profit margin. Therefore, there is little incentive for companies to compete by setting prices below the reference price. In fact, there is some evidence that companies increase the prices of products initially priced below the reference price to match the reference prices. (Danzon and Ketcham 2004; Puig-Junoy 2007.) In Finland, a maximum wholesale price is set for products that are included in the reference price system. In the fourth quarter price notification in 2017, approximately 32% of the products subject to reference pricing were priced to the level of the maximum wholesale price.

The demand for pharmaceuticals is relatively inelastic. Across several studies, price elasticity has been observed to range from −0.2 to −0.6 indicating that an increase of 10% in cost sharing would be associated with a 2 to 6% decline in prescription drug use or expenditures. Less price sensitivity is observed in pharmaceuticals used for chronic conditions than in pharmaceuticals used for acute conditions. (Manning et al. 1987; Contoyannis et al. 2005; Simonsen et al. 2016.) On the other hand, studies examining the association between reference pricing and pharmaceutical use and spending found large increases in the use of pharmaceuticals priced at or below the reference price and sharp declines in the use of higher-priced pharmaceuticals that require patient cost sharing. (Goldman et al. 2007.) During the first year of the reference price system in Finland, patients rejected substitution in 33% of the cases when the prescribed product's price was above the reference price. Physicians reject substitution only very rarely, in less than one percent of the purchases. (Saastamoinen et al. 2010.) In 2014, substitution was rejected in 6% of all purchases of products subject to reference pricing (Martikainen et al. 2016).

Secondly, perfect competition assumes that the products in the market are homogeneous and, therefore, perfect substitutes for each other. Buyers show no preference for a product from a particular seller. (Begg et al. 2000b.) Originator companies have, as first movers, a product differentiation[9] advantage that enables them to hold substantial

9 Product differentiation leads to buyers perceiving products as unique. A distinction should be made between horizontally and vertically differentiated products. Horizontal differentiation occurs when the decision to purchase is made according to subjective preferences such as colours and shapes. Vertical differentiation occurs when there are measurable and qualitative differences. Most products contain both types of differentiation but the generic market sector resembles horizontal differentiation more closely. (Hotelling 1929; Shaked and Sutton 1982; Shaked and Sutton 1987; Caplin and Nalebuff 1991.) Product differentiation is applied increasingly in pharmaceutical markets. Strategies include new dosage forms, fixed drug combinations and new indications (Dubey and Dubey 2009).

market shares even after lower-priced generic products enter the market (Schmalensee 1982; Conrad 1983). First-mover differentiation advantage appears to hold also in the first generic entrant: a Canadian study observed an increase of about 30% in market share compared to other generics for at least four years (Hollis 2002).

In addition, patients can have brand preferences. In Spain, 13% of the population would not accept generics as substitutes for originator products (Costa Font et al. 2014). Even when generics are viewed positively, it does not necessarily result in generic uptake (Hassali et al. 2009). In Finland, generic uptake increased significantly after the implementation of the reference price system. However, some patients still chose to purchase originator products priced over the reference price. While female gender, higher age and higher income increased the probability of originator product choice in some active substances, the right to special reimbursement lowered it. (Haula et al. 2014.) This is understandable in light of the fact that rejecting substitution in a special reimbursement category purchase often has an even more significant impact on patients' out-of-pocket expenses in relative terms than forbidding substitution in a basic reimbursement category purchase.

Thirdly, perfect competition assumes that buyers are perfectly informed about the quality, utility and price of the product and of the substitute products. They also act rationally. There is no extra cost for the buyer to switch between products or to acquire information about products and their prices. (Begg et al. 2000b.)

Pharmaceuticals can be regarded as credence goods[10], where substantial information asymmetry exists between patients, physicians and manufacturers. In pharmaceutical markets, this information asymmetry is handled by assigning the assessment of the quality, and pricing when applicable, of a product to regulators. (Scott Morton and Kyle 2012.)

Even within the demand side, asymmetry exists as typically the prescribing physician and the dispensing pharmacist have more knowledge than the patient[11]. Furthermore, as the number of pharmaceuticals is vast and continuously changing, a prescribing physician, let alone a patient, can rarely keep up with the alternatives, their therapeutic values, and prices. Consequently, decisions on prescriptions are often made under imperfect information. (WHO 1997.) In a reference price system,

10 Credence goods refers to situations where an expert knows more than the customer about the need and quality of goods and services a customer requires. There is great information asymmetry between the buyer and seller. Possible problems arising from this information asymmetry include, for instance, undertreatment and overtreatment, overcharging and excessive pricing. (Darby and Karni 1973; Dulleck and Kerschbamer 2006.)

11 The relationship between a patient and a physician is referred to as an agency relationship where the assumedly better-informed agent, the physician, acts on behalf of the assumedly less informed principle, the patient (Buchanan 1988). Presuming that the physician, acting as an agent, aims to maximize the patient's utility, his prescription choice should be the least costly one among equally effective choices, though taking into account patient preferences. It has been reported that while physicians do show sensitivity to patient costs and cost-sensitivity, it happens only when the cost differences between the choices is significantly high (Carrera et al. 2018).

regulators have clustered together products with a similar therapeutic effect and set a maximum reimbursement, or a reference price, to these products. There is no extra cost for a patient to switch between these products. In addition, pharmacies are obliged to provide guidance and information to patients in regard to the products and their prices.

Lastly, the perfect competition theory assumes is that there is free entry and exit to the market. There would be no patents or other exclusive rights. In addition, the government or other authorities would not restrain competition with, for instance, tariffs, subsidies or trade restrictions. (Begg et al. 2000b.)

The pharmaceutical industry is one of the most regulated industries. Regulation applies to research and development, to marketing authorization and, in most countries at least in some form, to reimbursement and pricing. Patents are an essential part of the industry. Market entry for generic products is typically easier than for originator products. This is, among other things, because the research and development process for a generic product is much quicker and less expensive than for an originator product and because explicit pricing regulations for generic products are often in place. Also in Finland, the process of gaining reimbursement status and a confirmed price is typically a quicker process for generic products than for originator products (Pharmaceuticals Pricing Board 2015).

Barriers to entry include access to distribution channels (Porter 1980). In practice, there are two wholesalers for pharmaceuticals in Finland. One-channel distribution is the prevailing practice though any law or regulation does not impose it. There is no fixed wholesale mark-up, so each company must negotiate it by themselves. The mark-up is not public knowledge but it is estimated to range between 1 and 20%, large companies having an advantage over small ones. (Valliluoto 2012.) Pharmacies are responsible for the retail sales of pharmaceuticals in Finland. At the end of 2016, there were 810 pharmacy outlets in Finland (The Association of Finnish Pharmacies 2017). Pharmacies are required to keep a sufficient stock of medicines, including products at or under reference price, in hand. They are also obliged to provide patients with information on medicine prices and, on request, to order products from a wholesaler.

Perfect competition is a hypothetical market structure that is seldom, if ever, achieved. In real life, particularly in the pharmaceutical markets, competition is always somewhat imperfect. However, perfect competition can be used as a benchmark to compare between pharmaceutical market structures. (Begg et al. 2000a.) In Table 3 (p. 33), perfect competition conditions and the conditions in the generic market sector under a reference price system are reviewed.

Table 3. Conditions for perfect competition and the conditions of generic pharmaceutical markets subject to reference pricing.

Perfect competition condition	Conditions of generic pharmaceutical markets subject to reference pricing
1. Large number of buyers and sellers • All with a relatively small market share • All price-takers • Price determines willingness to consume	Potentially a large number of sellers Large companies often have an advantage over smaller ones → Typically concentrated markets No incentive for price-sensitivity at prices below reference prices Prices have a tendency to increase towards maximum prices Inelastic demand, though less in a reference price system
2. Products are homogeneous • No preferences	Regulators define which products are homogeneous[a] Product differentiation and first mover advantage exist → Some patients exhibit brand loyalty and preferences → Also prescribing physicians and dispensing pharmacies can exhibit brand loyalty and preferences
3. Buyers are perfectly informed • No extra cost to switch between products or to acquire information	Substantial information asymmetry exists between patients, physicians, pharmacists and manufacturers → Patients are not perfectly informed about the qualities of a product, the associated utilities and prices Pharmacies are obliged to offer information about prices → There is no extra cost to switch between products
4. Free entry and exit to the market • Equal entry to distribution channels	Highly regulated markets → Concessions to generic medicines Large, established companies can have an advantage in regard to entry to distribution channels

[a] While generic products must have the same active substance, strength, dosage form, and route of administration as the originator products, they do not need to contain the same inactive substances. They may also differ in color and shape. However, the bioequivalence, i.e. the performance, of the generic product compared to the originator product must be proven. (Kesselheim et al. 2008.)

In circumstances with no free entry to the market, the power to set up prices concentrates in the hands of few companies. Indeed, even after generic competition has begun, monopolistic markets often persist or oligopolistic markets appear. (Puig-Junoy 2005.) In an oligopoly, there are only few sellers competing in the market. While there is no exact threshold for the number of competitors in oligopolistic markets, a rule of thumb is that an oligopoly exists when four or less companies account for more than 60% of the total market sales (Selten 1973; Shepherd 1997).

Aside from perfect competition, other theories propose that the same efficiency can be reached with other market structures. For example, according to the theory of contestable markets, perfect competition prices and output can be reached with just a few of the perfect competition assumptions. In contestable markets, the short-term threat from potential competitors provides such pressure over the present market holders that a competitive price is reached even with a relatively small number of sell-

ers. (Baumol 1982.)[12] Furthermore, according to Bertrand's duopoly model, oligopolistic markets can reach the same prices as perfect competition markets as long as the sellers in oligopolistic markets compete by changing their prices, not the quantities offered (Singh and Vives 1984).

12 To prove the threat of new entrants, this theory places special attention on free entry to and exit from the market. While inside the market, the new entrant should have the same advantages as the present market holder/-s. Also, the reaction time to changes for the present market holders should be longer than the time for a new firm to enter the market. In addition, consumers respond instantly to price differences. (Baumol 1982; Dixit 1982.)

6 Previous literature on the impact of a reference price system on pharmaceutical prices

A literature search was performed to identify previous literature on the impact of a reference price system on prices and expenditures of pharmaceuticals subject to the system. A substantial body of literature, including previous literature reviews, was identified. Of the earlier literature reviews, one of the most recent was by Acosta et al. (2014). A systemized literature search to update their literature review was performed. The used databases included Medline, EMBASE, EconLit, The Cochrane Library, PAIS Index and Sociological Abstracts (between 1 January 2011 and 10 February 2017). The used search terms were: reference pricing, reference price system/-s, prices and costs. Studies were eligible for inclusion in the supplementary review if the impact of internal reference pricing on prices or expenditures was studied using empirical data. The supplementary literature search strategy is presented in the Appendix.

Acosta et al. (2014) identified 13 studies analyzing the impact of a reference price system on pharmaceutical prices or expenditures. The supplementary search identified six relevant new studies, two of which were our own studies (Koskinen et al. 2014; Koskinen et al. 2015) and therefore not included in this summary. Of the remaining four studies, two reported results from the same study. The main results of the studies Acosta et al. (2014) refer to and the studies found in the supplementary search are presented in Table 4 (p. 37).

According to the literature, the implementation of a reference price system reduces the prices of drugs subject to the system. This result seems to be rather universal across different reference price systems and countries. The only deviations from this result come from two studies, one from Canada (Grootendorst et al. 2002) and the other from the US (Kibicho and Pinkerton 2012), countries with quite different pricing and regulatory systems compared to the European systems. In the other included studies, the price decrease was even close to 50% (Grootendorst et al. 2002; Marshall et al. 2002; Grootendorst et al. 2005; Kaiser et al. 2014), most of the impact seen soon after the implementation of a reference price system (Grootendorst et al. 2002). There were large differences between pharmaceutical groups. Results from Denmark suggest that a reference price system is likely to reduce only the prices of long-term treatment drugs (Kaiser and Mendez 2015). While this assumption was not tested in the other studies, several studies found that price decreases were greater for originator products than for generic products (Aronsson et al. 2001; Pavenik 2002; Brekke et al. 2011). This trend is comprehensible in light of the fact that generic products have typically lower prices than originator products. Therefore, originator products face a greater threat of losing market shares when a reference price system is implemented. However, the results from Denmark were the opposite; the prices of generic products decreased more than the prices of originator products (Kaiser et al. 2014; Kaiser and Mendez 2015).

The implementation of a reference price system also reduces pharmaceutical expenditures and the amount third party payers spend on medicines overall (Sawyer 1983; Schneeweiss et al. 2002b; Schneeweiss et al. 2003; Grootendorst et al. 2005; Puig-Junoy 2007; Moreno-Torres et al. 2011). These results apply to the short term, longer terms effects are uncertain. However, relative to the total pharmaceutical expenditures, the savings achieved with a reference price system can remain moderate. For example, in Spain the implementation of a reference price system led to a saving of 1.5% in annual total pharmaceutical expenditure (Moreno-Torres et al. 2011). This might be explained by evolving drug therapies; by the time drugs approach the off-patent state, new treatments have already started entering the market, often in significantly higher prices. In addition, while even significant decreases in prices can be achieved, the overall share of the products included in the reference price system, relative to the total pharmaceutical expenditures, is often low and therefore only moderate total savings are accumulated.

In six of the included studies, a therapeutic reference price system was adopted, in nine a generic reference price system, and in one study both systems. In the study where both systems were evaluated (Grootendorst et al. 2005), the therapeutic reference price system generated larger relative decreases in drug expenditure level. This is potentially explained by the pre-policy price difference of products included in the same reference groups; the broader the groups are, the more likely there is to be substantial price differences between the grouped products. Therefore, also larger decreases in total expenditure can be achieved.

Table 4. Literature on the impact of a reference price system on pharmaceutical expenditures and prices. Type and details of the systems and the main results.

Author-/s, year	Country (Area)	Study period - intervention follow up	Drugs included in analysis	Type of RPS	Specifics of the system		Main results
					Scope	Reference price	
Studies from Acosta et al. 2014							
Aronsson et al. 2001	Sweden	1993–1996 48 months	12 chemical substances (allopurinol, atenolol, cimetidine, clomipramine, diazepam, furosemide, indomethacine, naproxen, paracetamol/codeine, pindolol, propranolol and timolol)	GRP	National public insurance	10% higher than the price of the least expensive generic substitute	Originator product prices tend to decrease more than generic prices. Estimated price decreases about 47%.
Brekke et al. 2011	Norway	2003 12 months	8 chemical substances (amlodipine, cetirizine, citalopram, enalapril, omeprazole, lisinopril, loratidin and simvastatin)	GRP	National public insurance	Sales weighted average of originator and generic prices	Generic drug prices decreased by 13% and originator drug prices by 23%. Originator market share reduced by 15%.
Grootendorst et al. 2001; Grootendorst et al. 2002	Canada	1995–1999 1) 43/44 months 2) 17 months	Cardiovascular drugs (nitrates, ACE inhibitors and CCBs)	TRP	Public drug subsidy programme, senior citizens	1) Nitrates: Price of lowest priced product 2) ACE inhibitors and CCBs: Price of the least-expensive product	1) Nitrates: Prices decreased by 47–50%. 2) ACE inhibitors: Prices increased from 1 to 5%. CCBs: Prices decreased from –14 to –19%. Impact on expenditure greatest right after implementation.

Table 4 continues.

Table 4 continued.

Author-/s, year	Country (Area)	Study period - intervention follow up	Drugs included in analysis	Type of RPS	Specifics of the system		Main results
					Scope	Reference price	
Grootendorst et al. 2005	Canada	1994–2001 1) 87 months 2) 68 months	Drug class NSAIDs	1) TRP 2) GRP	Public drug subsidy programme, senior citizens	1) The average of the lowest cost drugs 2) Less costly NSAIDs fully reimbursed	TRP cut annual expenditures by half. The impact of GRP about one-quarter of the impact of TRP.
Grootendorst and Stewart 2006	Canada	1997–2000 48 months	Cardiovascular drugs (ACE inhibitors and CCBs)	TRP	Public drug subsidy programme	Typically equal to the price of the lowest-cost interchangeable drug	Decrease in expenditure on ACE inhibitors 9%, and on CCBs 7.8%.
Kibicho and Pinkerton 2012	US	2003–2004 11 months	Antihypertensive and anti-hyperlipidemic	GRP	Medicaid programme, senior citizens	Equal to other third party insurers and states	Increase in daily cost, though insignificant. Generic prices reduced, but no increase in generic market share.
Marshall et al. 2002	Canada	1995–1999 44 months	Hyperacidity drugs (H_2RAs)	TRP	Public drug subsidy programme, senior citizens	Cost of the least expensive H_2RA available	Expenditures on H_2RAs decreased by 38% after 6 months and by 34% after 2 years.
Moreno-Torres et al. 2011	Spain (Catalonia)	2000–2006 1) 48 months 2) 36 months	Off-patent drug groups	GRP	National public insurance	1) Weighted average price of the cheapest drug with at least 20% of the market 2) Average of the three lowest costs per day of treatment	1) No significant impact. 2) Annual saving of 1.5% in total pharmaceutical expenditure.

Table 4 continues.

Table 4 continued.

Author-/s, year	Country (Area)	Study period - intervention follow up	Drugs included in analysis	Type of RPS	Specifics of the system		Main results
					Scope	Reference price	
Pavcnik 2000; Pavcnik 2002	Germany	1989–1996 36/60/132 months	Oral antidiabetics and anti-ulcer drugs	TRP	National statutory health insurance	Typically below the price of the most expensive brand but above the prices of the generics	Generics: prices decreased on average by 10%. Originators: prices decreased on average by 26%.
Puig-Junoy 2007	Spain	2001–2004 1a) 19 months (lovastatin) 1b) 10 months (lovastatin and simvastatin) 2) 38 months	Statins (atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin and simvastatin)	1a & 1b) GRP 2) GRP (all statins with more than two products on the market)	1a & 1b) National public insurance 2) Regional public insurance (Andalusia)	1a) Weighted average of the lowest priced products accounting at least 20% of the market volume 1b) Average of the three lowest costs per day of treatment 2) Higher price of the two lowest-priced products (requires generic prescribing)	1a) Lovastatin: Mean monthly saving in first year 16.7% (1.1% of total statins sales). 1b) Lovastatin: Mean monthly saving 16.3% (0.7% of total statin sales). Simvastatin: Mean monthly saving 51.8% (13.9% of total statin sales). 2) Non-significant savings in the full observation period.
Sawyer 1983	USA (State of Maryland)	1976–1979 38 months	52 dosage forms of 25 multisource chemical entities (incl. ampicillin, chlordiazepoxide, penicillin, proposyphene and tetracycline)	GRP	Regional public insurance	Lowest of the estimated purchase prices (+ a flat dispensing fee) paid by retail pharmacists.	A significant, but short-lived, decline in pharmaceutical spending levels observed.
Schneeweiss et al. 2002a; Schneeweiss et al. 2002b; Schneeweiss et al. 2002c	Canada (Province of British Columbia),	1997–1998 16 months	ACE inhibitors	TRP	Regional public drug subsidy programme, senior citizens	Price of the least-expensive product	A decline of 29% in the use of higher-priced cost-shared ACE inhibitors. After 16 months, the mean monthly expenditure per patient 19% lower than forecasted from pre-policy trend.

Table 4 continues.

Table 4 continued.

Author-/s, year	Country (Area)	Study period - intervention follow up	Drugs included in analysis	Type of RPS	Specifics of the system		Main results
					Scope	Reference price	
Schneeweiss et al. 2003	Canada (Province of British Columbia)	1997–1998 16 months	CCBs	TRP	Regional public drug subsidy programme, senior citizens	Price of the least-expensive product	No systematic change in drug prices per median monthly doses. After 6 months, the mean monthly expenditure per patient 12% lower than forecasted from pre-policy trend.
Identified new studies							
Ghislandi et al. 2013	Italy	1999–2009 126 months	Six therapeutic groups (ACE inhibitors, antidepressants, beta-blocking agents, CCBs, GORD and statins)	GRP	National health plan	Lowest available price	Prices in groups subject to GRP dropped 13% more than in groups not subject to it. Each entry of a new generic: a price drop of around 2.8%.
Kaiser et al. 2013; Kaiser et al. 2014	Denmark	2005–2007 14/26 months	Statins	GRP	National health insurance	The cheapest price	21% price decrease after 14 months and 48% after 26 months. Smaller price decreases for branded products; generic prices –36%, originator prices –7% and parallel import prices –19% after 26 months.
Kaiser and Mendez 2015	Denmark	2005–2006 17 months	Three therapeutic classes (anticholesterols, antiulcerants and antibiotics)	GRP	National health insurance	The cheapest price	Substantial price decreases for lifelong treatment, less substantial for medium duration treatment, and no significant effects for acute treatments. No impact on original product or parallel import prices, only on generic prices.

Abbreviations: ACE inhibitors = angiotensin-converting-enzyme inhibitors, CCBs = calcium channel blockers, GORD = drugs for gastro-oesophageal reflux disease), GRP = generic reference pricing, H_2RAs = histamine$_2$ receptor antagonists, ISDN = isosorbide dinitrate, NSAIDs = nonsteroidal anti-inflammatory drugs, TRP = therapeutic reference pricing.

7 Rationale of the study

Pharmaceutical expenditures rose in a rapid pace during the late 1990s and early 2000s. Soon thereafter, most European economies were faced with a financial downturn and, consequently, a need to cut down public expenditures on pharmaceuticals was evident (Leopold et al. 2014). This was accurate also in Finland where antidepressants and antipsychotics were, in terms of value, among the most rapidly growing pharmaceutical groups. However, studies analysing the exact reasons behind the overall growth trend and specifically the antidepressant and antipsychotic growth trend in Finland were missing. Understanding the reasons behind pharmaceutical expenditures and its growth is vital in evaluating the success of taken cost containment methods, which makes it an important subject for research.

According to existing literature, reference price systems are associated with decreases in the prices of products subject to the system. However, the size of the impact differs between systems and drug groups. In the existing literature, the focus has mainly been on cardiovascular, antihypertensive and antiulcerant drugs (Acosta et al. 2014) while there are no studies assessing the impact of reference pricing on antipsychotic drugs, one of the drug groups with the fastest growth trends. Therefore, it was considered an important drug group for research. Later on, in order to get a more generalized picture, the study was expanded to include other drug groups.

In existing literature, there are no studies where the impact of generic substitution has been isolated from the impact of reference pricing. This assessment would be important from both a theoretical and a policymaking perspective. As generic substitution and reference pricing were implemented separately in Finland, isolating the impacts from each other was possible. Furthermore, several studies have investigated the impact of a reference price system on prices and expenditures (Ghislandi et al. 2013; Acosta et al. 2014; Kaiser et al. 2014; Kaiser and Mendez 2015), and some on health and the use of healthcare services (Schneeweiss et al. 2003; Stargardt 2009). However, relatively little is known about the impact of reference price systems on market structure and competition within the market, or about the evolution of the system. It is known from other health care reforms that an impact tends to wane as time passes. This was considered an important issue to investigate also in regard to reference price systems.

8 Aims of the study

The objective of this study is to examine the impact of a reference price system on prices and the competitiveness of the market. A specific focus is on a pharmaceutical group where the growth in expenditure before the implementation of the reference price system was especially high, namely antipsychotics. In this thesis, the impact of reference pricing on competition is reflected upon through perfect competition conditions.

The more specific aims of the four substudies were as follows:

i. To analyse the factors behind growing antipsychotic and antidepressant costs in outpatient care in Finland before the implementation of a reference price system (Publication I).
ii. To analyse the short-term and the medium-to-long-term impact of the implementation of a reference price system on antipsychotic prices. The additional impact of reference pricing on previously implemented generic substitution is also assessed. (Publications II and III.)
iii. To analyse the impact of a reference price system on prices, competition and market structure of 12 different active substances (Publication IV).

9 Materials and methods

9.1 Data sources and study designs

The data for this study was collected retrospectively from Kela's prescription register and the official price lists of pharmaceutical products. The prescription register is maintained by Kela and it contains information on medicine purchases reimbursed under the National Health Insurance scheme. The register extensively covers the prescription medication consumption in outpatient care in Finland. For example, the register covers well over 90% of the ambulatory consumption of antipsychotics. For each reimbursed purchase, the prescription register contains detailed information about the patient (e.g. unique personal identification code, age, gender, place of residence), the purchased product (e.g. the Anatomical Therapeutic Chemical (ATC) code, the Nordic commodity number, the tradename, marketing authorisation holder, strength, form), costs (e.g. the total costs and the reimbursement part of the costs, reference prices), reimbursement categories, the number of packages and defined daily doses (DDDs) purchased, whether the product is included in generic substitution or reference pricing, and whether the patient or the physician have rejected the substitution. The concept of DDD was developed for drug consumption statistics, and it represents the typical daily dose for a drug when it is used for its main indication in adults (WHO Collaborating Centre for Drug Statistics Methodolgy 2018). As the prescription register does not include information on the actual prescribed dosages, DDDs are used as a proxy for the daily dosage.

Kela also maintains the official pharmacy price list. Companies that have products subject to price notification under the reference price system give quarterly price notifications to Kela. These price notifications are used to determine reference prices. Additional price notifications can be given every two weeks. The pharmacy price list also contains the prices of products not subject to the reference price system. (Kela 2017a.)

The prescription register was used as a data source in all four publications. While the study period differed between the publications, the total timeframe of the retrieved prescription register data span from January 1999 to October 2013. In the fourth publication, a pharmacy price list (from March 2009 to October 2013) was also used.

In the first publication, the studied medicine groups were antipsychotics and antidepressants as a whole. In the second publication, the antipsychotics clozapine, olanzapine, quetiapine and risperidone were studied in more detail. All four active substances were included in the reference price system in April 2009. Clozapine and risperidone had been included in generic substitution before inclusion in the reference price system, clozapine in January 2006 and risperidone in January 2008. For each active substance, the most used substitution group was identified and selected. In the third publication, olanzapine, quetiapine and risperidone were studied along

with a control group, aripiprazole, an antipsychotic drug not subject to either generic substitution or the reference price system.

The twelve active substances studied in the fourth publication were included in generic substitution and the reference price system simultaneously between April 2009 and October 2010. Of these, the antipsychotics olanzapine and quetiapine, were included into the schemes in 2009. The remaining 10 active substances were included in the schemes in 2010. Also in this study, the most used substitution group for each active substance was identified and selected.

9.2 Statistical methods

In order to study the research questions described in Chapter 8, statistical multivariate models with selected explanatory variables were developed for each research question. The research questions, data and used statistical methods for each publication are presented in Table 5 (p. 48).

9.2.1 Decomposition analysis of factors behind growing pharmaceutical costs (Publication I)

To analyse the factors behind growing pharmaceutical costs, a decomposition model was formed. In the model, the realized total costs (Totcost) of a drug class (e.g. ATC group X) in any year (t) are explained by four factors. The four explanatory factors are: (1) the size of the population (Pop), (2) the proportion of patients per population (*Pat/pop*), (3) the average amounts consumed per patient measured as defined daily doses (*DDD/Pat*), and (4) the average cost per one day of treatment (*Cost/DDD*). Formally, the model can be expressed as:

$$Totcost_{Xt} = Pop_t \times (Pat_{Xt}/Pop_t) \times (DDD_{Xt}/Pat_{Xt}) \times (Cost_{Xt}/DDD_{Xt}) \quad (1)$$

The changes in the four factors affecting the cost growth and their relative effect on the cost growth were analysed. The relative effect of each factor was calculated by dividing the growth (%) of this factor by the sum of the changes (%) of all the factors with a positive growth trend. Factors with a negative growth trend were not assessed.

9.2.2 Segmented linear regression analysis of an interrupted time series (Publications II and III)

In an interrupted time series, data is collected at multiple time points before and after an intervention. In segmented regression analysis, the time series is divided into pre- and post-intervention segments. The model estimates the level and the trend of the outcome of interest in the pre-intervention segment and then estimates the changes in level and trend in the subsequent post-intervention segment or segments. (Wagner et al. 2002; Zhang et al. 2009.) This can be expressed as:

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times intervention_t + \beta_3 \times time\ after\ intervention_t + \varepsilon_t \quad (2)$$

In the model, Y is the outcome of interest in time point t. *Time* is a continuous variable indicating time points at time t from the start of the observation period. *Intervention* is an indicator for time t, coded 0 before the intervention and 1 after it. *Time after intervention* receives a value of 0 before the intervention and is a continuous variable indicating time points after the intervention. β_0 estimates the baseline level of the outcome. β_1 estimates the baseline trend, that is, the change occurring with each time point before the intervention. β_2 estimates the level of change in the outcome immediately after the intervention. β_3 estimates the change in the trend of the outcome after the intervention, compared with the trend before the intervention. ε is the error term.

The results can be presented as parameter estimates and as absolute and relative differences between estimated post-intervention values at given time points compared with estimated values had the intervention not been implemented.

The model can also specify more than one intervention or change point. A model with two interventions would be:

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times intervention1_t + \beta_3 \times time\ after\ intervention1_t + \beta_4 \times intervention2_t + time\ after\ intervention2_t + \varepsilon_t \quad (3)$$

The design can be further strengthened by adding a control group. In this design, the model can also specify more than one intervention or change points. A model with one intervention and a control group would be:

$$Y_t = \beta_0 + \beta_1 \times time_t + \beta_2 \times intervention_t + \beta_3 \times time\ after\ intervention_t + \beta_{\Delta 0} C + \beta_{\Delta 1} C \times time_t + \beta_{\Delta 2} C \times intervention_t + \beta_{\Delta 3} C \times time\ after\ intervention_t + \varepsilon_t + \varepsilon_{Ct} \quad (4)$$

Here, Δ denotes the estimated difference between the intervention group and the control group. For example, $\beta_{\Delta 0}$ estimates the difference between the intervention group and the control group in the baseline level. C is an indicator for group, coded 0 for the intervention group and 1 for the control group.

In this study, interrupted time series design and segmented linear regression analysis were used to estimate the effect of the implementation of generic substitution and a reference price system on the daily cost of antipsychotics, measured as cost per DDD. In the dataset, there were 39 monthly pre-reference pricing time points in both the short-term and the medium-to-long-term models. For risperidone, the 39 months before reference pricing could be further divided into 24 months before and 15 months after the introduction of generic substitution. Therefore, generic substitution and reference pricing were included as separate interventions in the risperidone

model. In the short-term analysis, there were 12 monthly post-reference pricing time points and in the medium-to-long-term analysis 30 monthly post-reference pricing time points. Aripiprazole, an antipsychotic not subject to generic substitution or reference pricing, was added to the medium-to-long-term model as a control group.

As error terms may be correlated in time series data, a Durbin-Watson test was applied. Autocorrelation was detected in all of the datasets, and thus autoregressive error models were used to estimate the regression parameters with control of autocorrelation. The autoregressive error model is given by:

$$\nu_t = -\varphi_1 \nu_{t-1} - \ldots - \varphi_n \nu_{t-n} + \varepsilon_t \qquad \varepsilon_t \sim IN(0, \sigma^2) \tag{5}$$

Here, the error term ν consists of an autoregressive error part $-\varphi_1 \nu_{t-1} - \ldots. - \varphi_n \nu_{t-n}$ and a random error part ε_t.

In addition, the normality and homoscedasticity of the residuals were checked by statistical tests and a graphic analysis of residuals was performed. While statistical tests supported the assumption of heteroscedasticity in the olanzapine data, the scatter plot of times and residuals suggested the possibility of heteroscedasticity in the variable time. Thus, a model without a time variable was also fitted for the olanzapine data. Furthermore, an abrupt increase in the daily cost of olanzapine was seen in the medium-to-long term data, 15 months after the implementation of the reference price system. This increase, which was not caused by any health policy intervention, was included in the olanzapine medium-to-long term model as a second change point, the first being the implementation of reference pricing.

A departure from the assumption of the homoscedasticity of the residuals was detected in the risperidone data. An outlier was found to be the source of the heteroscedasticity. The outlier was identified as the month preceding the implementation of generic substitution, which implies that the manufacturers were anticipating the forthcoming reform. A dummy variable estimating the pre-effect on generic substitution was constructed for the risperidone model. The confidence intervals for absolute and relative changes in the daily cost were calculated using bootstrap methods.

9.2.3 Price competition analysis and market concentration (Publication IV)

A regression model was built to analyse the impact of the reference price system on price competition in the generic market sector in Finland. Six explanatory factors were used to analyse the impact of the reference price system on prices (*Price*) in any reference price period (*t*): inclusion in the reference price system (*RPS*), time from inclusion in the reference price system (*time*), number of competitors (*no*), the market share of the market leader (*dom*), patients' copayment rate (*cop*) and firms' experience of the markets under the reference price system (*exp*). For each substitution group a price index was used to follow the price developments for a three-year

follow up period. The base period was the month before the substitution group was included in the reference price system. For the following periods, the indices were based on the reference price of the substitution group in question. Statistical tests and graphic analyses were performed to detect any deviations from the assumptions of linear regression. As multicollinearity was detected, the time variable was squared ($time^2$). Autocorrelation was also detected and, thus, the error term (v) consists of an autoregressive and a random error part. The model can be expressed as:

$$Price_t = \beta_0 + \beta RPS_t + \beta time_t^2 + \beta no_t + \beta dom_t + \beta cop_t + \beta exp_t + v_t \quad (6)$$

Furthermore, the competitive conditions of the market were measured with the Herfindahl-Hirschmann Index (HHI). The index combines the number of competitors (no) and their respective market shares into a single concentration index. In this study, the HHI for each active substance is calculated as follows:

$$HHI_{active\ substance} = \sum_{i=1}^{no} \left(\frac{q_i}{A}\right)^2 \quad (7)$$

q_i is the number of purchases of company *i's* product in the most used substitution group in the active substance in question and A is the sum of all purchases in the substitution group in question. Therefore $\frac{q_i}{A}$ is the market share of company i in the most used substitution group of the active substance in question. The index receives values ranging from 0, which indicates perfect competition, to 10,000 which in turn indicates monopoly. The lower the value is, the higher is the competitiveness of the market. When the index is lower than 1,500 the market is considered unconcentrated. An index between 1,500 and 2,500 means the market is moderately concentrated, and with an index above 2,500, the market is described as highly concentrated. (US Department of Justice and the Federal Trade Commission 2010.)

Table 5. Research questions, data and methods by publication number.

	Publication I	**Publication II**	**Publication III**	**Publication IV**
Research question/-s	What are the explicit factors behind ambulatory antipsychotic and antidepressant cost growth in Finland? What is the relative importance of the factors in drug group specific cost growth?	What is the impact of the RPS on the daily cost of antipsychotic drugs in Finland in the short term? What is the additional impact of the RPS on previously implemented GS?	What is the impact of the RPS on the daily cost of antipsychotic drugs in Finland in the medium- to long-term? What is the additional impact of the RPS on previously implemented GS?	What is the impact of the RPS on price competition and pharmaceutical market structure in Finland? What are the factors associated with price competition?
Study period	1 Jan 1999 – 31 Dec 2005	1 Jan 2006 – 31 Mar 2010	1 Jan 2006 – 31 Sep 2011	1 Mar 2009 – 31 Oct 2013[a]
Data sources	Prescription register	Prescription register	Prescription register	Prescription register Pharmacy price list
Studied medicine groups (ATC codes)	N05A antipsychotics N06A antidepressants	N05AH02 clozapine N05AH03 olanzapine N05AH04 quetiapine N05AX08 risperidone	N05AH03 olanzapine N05AH04 quetiapine N05AX08 risperidone N05AX12 aripiprazole	B01AC04 clopidogrel C07AB08 celiprolol C08CA13 lercanidipine C09CA03 valsartan C10AA07 rosuvastatin G03CX01 tibolone G04BE03 sildenafil L01AX03 temozolomide N05AH03 olanzapine N05AH04 quetiapine N06AB10 escitalopram S01ED51 timolol in combination
Methods	Decomposition analysis	Segmented linear regression analysis of interrupted time series	Segmented linear regression analysis of interrupted time series with a control group	Linear regression analysis
Response variable	Total costs of the study drug groups	Cost of one day of treatment	Cost of one day of treatment	Reference price index

Table 5 continues.

Table 5 continued.

	Publication I	Publication II	Publication III	Publication IV
Explanatory variables	1. Population 2. Patients per population 3. DDDs per patient 4. Average cost per DDD	1. Time from the beginning of the observation period (trend) 2. Implementation of GS or RPS or GS and RPS (level) 3. Time after the implementation of GS or RPS or GS and RPS (trend)	1. Time from the beginning of the observation period (trend) 2. Implementation of GS or RPS or GS and RPS (level) 3. Time after the implementation of GS or RPS or GS and RPS (trend) 4. Manufacturers' price increase (level) 5. Time after manufacturers' price increase (trend) • all variables are calculated both for observation and control group • factors 4 and 5 apply to the olanzapine long term model	1. Inclusion in the RPS 2. Time from inclusion in the RPS in months 3. Number of competitors 4. Market share of the market leader 5. Copayment rate 6. Firms' experience of the market
Additional analyses				Market concentration measured with the Herfindahl-Hirschmann Index (HHI)

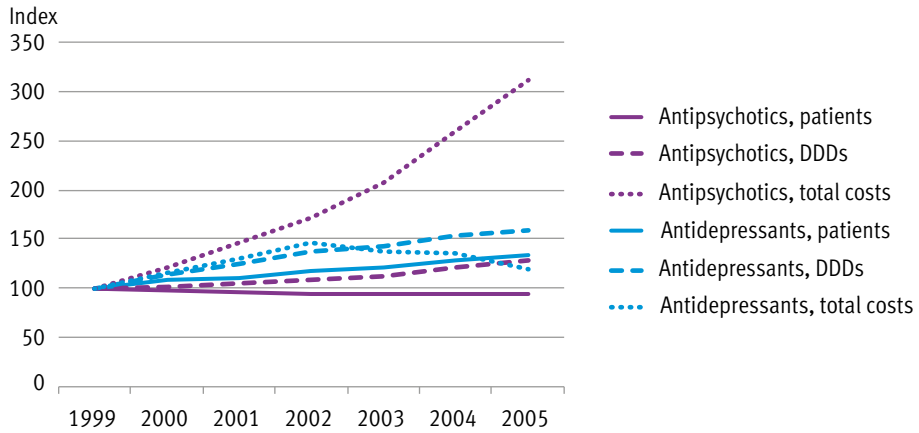
[a] For each active substance the data collection started a month before the active substance was included in the reference price system and ended three years after inclusion.
DDD = defined daily dose, GS = generic substitution, RPS = reference price system.

10 Results

10.1 Factors associated with pharmaceutical cost growth (Publication I)

From 1999 through 2005, the cost growth of reimbursed purchases was 211% for antipsychotics and 19% for antidepressants. In euros, the increase was from 29 million euros to 90 million euros for antipsychotics and from 54 million euros to 65 million euros for antidepressants. Deflating the costs to 2005 money, decreased the cost growth of reimbursed purchases of antipsychotics and antidepressants to 183% and 8.5%, respectively. At the same time, the proportion of antipsychotic users in the total population decreased from 2.4% to 2.2% while the proportion of antidepressant users increased from 4.8% to 6.3%. However, the amount of defined daily doses purchased increased in both groups. (Figure 5.)

Figure 5. Reimbursed antipsychotic and antidepressant purchases in Finland 1999–2005. Patients, defined daily doses (DDDs) and total costs presented as indices (1999 = 100).



Drug choices changed notably between 1999 and 2005, especially among antipsychotics. In 1999, second-generation antipsychotics accounted for 22% of the total consumption, while in 2005 their proportion had increased to 62%. In 2005, the most consumed antipsychotics were olanzapine and risperidone. The shift to new and more expensive second-generation antipsychotics also led to an increase in the mean daily cost of treatment, which more than doubled during the study years. In 1999, the mean daily cost of antipsychotic treatment was 1.37 euros while by 2005 it had risen to 2.94 euros.

Citalopram was the most consumed antidepressant throughout the study period. In the beginning of the study period, the consumption of other, newer antidepressants was low but it increased rapidly during the study years. However, contrary to antipsychotics, the mean daily cost of antidepressant treatment went down from 1.06 euros to 0.79 euros. This was due to the implementation of generic substitution in 2003,

which made the price competition for antidepressants possible. Antipsychotics were not included in generic substitution during the study years.

When analysing the factors affecting the growth in costs, we found that the two drug groups differed considerably. For antipsychotics, about 80% of the cost growth resulted from the rise in the mean daily cost of treatment while the increase in patients per population accounted for about 60% of the antidepressant cost growth. The growth in the size of the population had only a marginal effect on the cost growth while the amounts consumed per patient increased in both drug classes. The relative effect of these increases on the cost growth was about 19% for antipsychotics and about 38% for antidepressants. (Table 6.)

Table 6. Factors affecting the drug costs for antipsychotics and antidepressants in Finland, their change from 1999 to 2005, and their relative effects on cost growth.

	Antipsychotics		Antidepressants	
Factor	Change (%)	Relative effect on cost growth (%)	Change (%)	Relative effect on cost growth (%)
Population	1.6	0.9	1.6	3.1
Patients per population	−6.7	decreased	31.0	59.2
DDDs per patient	34.8	19.3	19.7	37.7
Average cost per DDD	143.6	79.8	−25.2	decreased
Total		100		100

DDD = defined daily dose.

While the factors affecting cost growth varied considerably between the two drug groups, even within the groups, there were some differences in the age- and gender specific cost growth drivers. For antipsychotics, the increase in patients per population was the most significant factor affecting the cost growth in the age group of under 20-year-olds. For men in this age group, the relative effect was about 48% and for women about 40%. For all other age groups, the most important factor affecting the antipsychotics cost growth was the cost per one day of treatment. For antidepressants, the increase in patients per population explained from 57% to 64% of the cost growth in the age group of under 40-year-olds. In older age groups, the increase in the size of the population, patients per population and amounts consumed per patient each explained approximately one third of the antidepressant cost growth.

10.2 The impact of the reference price system on pharmaceutical costs (Publications II and III)

The impact of the implementation of reference pricing on the daily cost of the antipsychotics olanzapine, quetiapine, risperidone and clozapine was analysed in Publications II and III. Olanzapine, quetiapine and risperidone were included in both

short-term and medium-to-long-term impact analyses, clozapine only in the short-term analysis. Risperidone was also used to analyse the additional impact of reference pricing on previously implemented generic substitution.

10.2.1 Medium-to-long-term impact of implementing the reference price system

There was a substantial decrease in the daily cost of antipsychotic medication after the implementation of reference pricing in Finland. In the medium-to-long-term analysis, the daily cost of the studied antipsychotics was 24.6% to 50.6% lower than it would have been were reference pricing not implemented. In absolute terms, this meant a reduction of approximately €1.00 for olanzapine, €1.97 for quetiapine and €3.09 for risperidone. (Table 7; Figure 6, p. 53.)

Table 7. Absolute and relative effects of the interventions on daily cost 12 and 30 months after the implementation of reference pricing, estimated from the regression models.

	Daily cost with intervention/-s, euros		Daily cost without intervention/-s, euros		Absolute change, euros (95% CI)		Relative change, % (95% CI)	
Active substance	12 months	30 months	12 months	30 months	12 months	30 months	12 months	30 months
Clozapine, RPS	1.5014	.	2.1430	.	−0.6416 (−0.8355, −0.4461)	.	−29.9 (−37.6, −21.8)	.
Olanzapine, both GS and RPS	1.5509	3.0579	4.6046	4.0535	−3.0537 (−3.3425, −2.7660)	−0.9956 (−1.2463, −0.7702)	−66.3 (−70.7, −61.8)	−24.6 (−29.8, −19.6)
Quetiapine, both GS and RPS	3.0917	1.9168	4.7482	3.8834	−1.6565 (−1.9443, −1.3670)	−1.9666 (−2.2959, −1.6386)	−34.9 (−39.8, −29.7)	−50.6 (−56.0, −44.6)
Risperidone, both GS and RPS	4.2045	4.0203	7.4093	7.1070	−3.2048 (−3.4034, −3.0069)	−3.0867 (−3.3622, −2.8090)	−43.3 (−44.9, −41.5)	−43.4 (−45.6, −41.1)
Risperidone, only GS	4.9940[a]	4.0487[b]	7.4093[a]	7.1070[b]	−2.4153[a] (−2.5919, −2.2331)	−3.0583[b] (−3.4834, −2.6319)	−32.6[a] (−34.4, −30.8)	−43.0[b] (−48.4, −37.6)

GS = generic substitution, RPS = reference price system, CI = confidence interval.

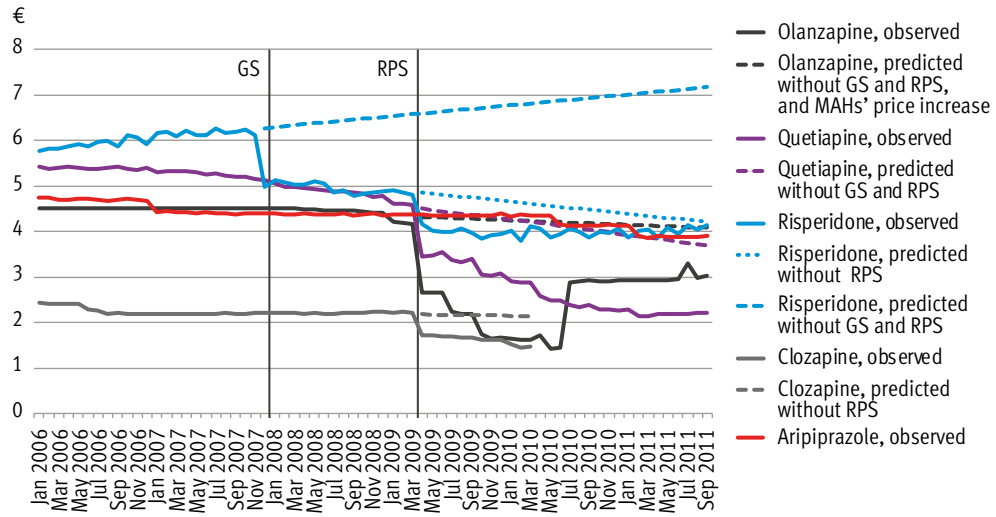
[a] Time since implementation of GS: 27 months.

[b] Time since implementation of GS: 45 months.

For olanzapine and quetiapine, there was a downward month-to-month trend preceding the implementation of reference pricing, followed with a substantial drop in the level of the daily cost immediately after implementation. While the month-to-month downward trend accelerated for both active substances, there was an abrupt increase of approximately €1.50 in the daily cost of olanzapine fifteen months af-

ter the implementation of reference pricing, and the month-to-month trend shifted from a downward to an upward direction. (Table 8, p. 54.) Changes in the number of companies operating in the olanzapine market explained the phenomenon. Until the implementation of reference pricing, one company had, in practice, a monopoly position in the market. At the implementation of reference pricing, there were four companies in the olanzapine market, though one soon exited. The three remaining companies were engaged in price competition until June 2010 when patent protection issues forced one of the companies to exit the market. The two remaining companies raised their prices immediately to the maximum wholesale price of the remaining generic product. After the originator brand's patent expired internationally in October 2011, more companies entered the market and price competition restarted.

Figure 6. The observed daily cost of olanzapine, quetiapine, risperidone and clozapine, and their predicted daily cost without the implementation of generic substitution and the reference price system[a].



GS = generic substitution, RPS = reference price system, MAH = market authorization holder.

[a] The observed daily cost is presented also for the control antipsychotic aripiprazole. For clozapine, the curve is based on short-term analysis and for the other antipsychotics, on medium-to-long-term analysis.

For risperidone, there was an upwards month-to-month trend before the implementation of generic substitution which resulted in a drop in the level of the daily cost. This drop was slightly less than the pre-effect one month before the implementation of generic substitution. A second drop in the level of the daily cost of risperidone was seen 15 months later when risperidone was included in the reference price system. However, while the month-to-month trend turned in a downward direction after the implementation of generic substitution, it reverted to an upward trend after the implementation of the reference price system in the medium-to-long-term model. (Table 9, p. 54.)

Table 8. The impact of reference pricing on the daily cost of olanzapine and quetiapine in Finland 12 and 30 months after the implementation of reference pricing[a].

	Olanzapine			Quetiapine		
	12 months	30 months		12 months	30 months	
Variable	Coefficient (€)	Coefficient (€)	Relative to aripiprazole	Coefficient (€)	Coefficient (€)	Relative to aripiprazole
Baseline level	4.9495	4.6485	NS	6.0130	5.6360	−0.9923
Monthly trend before reference pricing	−0.0068	−0.0086	NS	−0.0248	−0.0254	0.0179
Level change after reference pricing	−1.5789	−1.5251	1.5812	−1.0493	−1.1326	1.1633
Change in monthly trend after reference pricing	−0.1229	−0.0893	0.0908	−0.0506	−0.0278	0.0211
Level change after price increase	.	1.4940	−1.5236	.	.	.
Change in monthly trend after price increase	.	0.1143	−0.1322	.	.	.

[a] 30-month results are also presented relative to the control antipsychotic aripiprazole.

Table 9. The impact of separately implemented generic substitution and reference pricing on the daily cost of risperidone in Finland 12 and 30 months after the implementation of reference pricing[a].

	12 months	30 months	
Variable	Coefficient (€)	Coefficient (€)	Relative to aripiprazole
Baseline level	6.2567	5.8167	−1.0179
Monthly trend before generic substitution	0.0226	0.0187	−0.0380
Pre-effect to generic substitution	−1.4291	−1.2413	1.2970
Level change after generic substitution	−1.3164	−1.1233	1.1408
Change in monthly trend after generic substitution	−0.0407	−0.0430	0.0643
Level change after reference pricing	−0.7895	−0.8114	0.9266
Change in monthly trend after reference pricing	NS	0.0261	−0.0489

[a] 30-month results are also presented relative to control active substance aripiprazole.

10.2.2 Short-term impact of implementing the reference price system

After 12 months of the implementation of the reference price system, the daily cost of the studied antipsychotics (clozapine, olanzapine, quetiapine and risperidone) was

29.9% to 66.3% lower than it would have been were reference pricing not implemented. While the reduction of the daily cost for olanzapine was high, 66.3%, in the short-term model, the reduction was much less, 22.6%, in the medium-to-long-term model. This was due to changes in the number of companies in the market. For quetiapine, the reduction increased from 34.9% to 50.6%. As for risperidone, the reduction in daily cost was almost the same in both short-term and medium-to-long-term analyses, a little over 43%. (Table 7.)

Clozapine was only included in the short-term model. One year after the reference price system was implemented, the daily cost of clozapine was 29.9% lower than it would have been were reference pricing not implemented (Table 7, Figure 6). There was a slight downwards pre-reference pricing trend in the daily cost of clozapine, followed by a fall in the level of the daily cost immediately after the implementation and an acceleration in the month-to-month decreasing trend (Table 10).

Table 10. The impact of reference pricing on the daily cost of clozapine in Finland 12 months after the implementation of reference pricing.

Variable	Coefficient (€)
Baseline level	2.3008
Monthly trend before reference pricing	−0.0031
Level change after reference pricing	−0.4676
Change in monthly trend after reference pricing	−0.0145

10.2.3 The additional impact of reference pricing on previously implemented generic substitution

As risperidone was included in generic substitution and reference pricing at separate times during the study period, it was possible to isolate the impact of generic substitution from the subsequent impact of reference pricing on the daily cost of risperidone.

The baseline daily cost of risperidone was €5.82 in the medium-to-long-term model. 2.5 years after the implementation of reference pricing, the daily cost was estimated to be €4.02, which represents an absolute reduction of €3.09 and a relative reduction of 43.3%. Had only generic substitution been implemented, the daily cost was estimated to have been €4.05, representing an absolute reduction of €3.06 and a relative reduction of 43.0%. Therefore, the additional impact of the separately implemented reference pricing on previously implemented generic substitution was very low in the medium-to-long-term. (Table 7, Figure 6.) Also in the short-term, most of the decrease in the daily cost of risperidone was generated by generic substitution, over 75% of the total decrease observed at the end of the first year. After 2.5 years, the share was over 99%.

10.3 Competition and market structure in pharmaceutical markets under the reference price system (Publication IV)

In the fourth publication, the data was extended so that it included more pharmaceutical groups. In addition, the time span was extended to include the first three years of the reference price system.

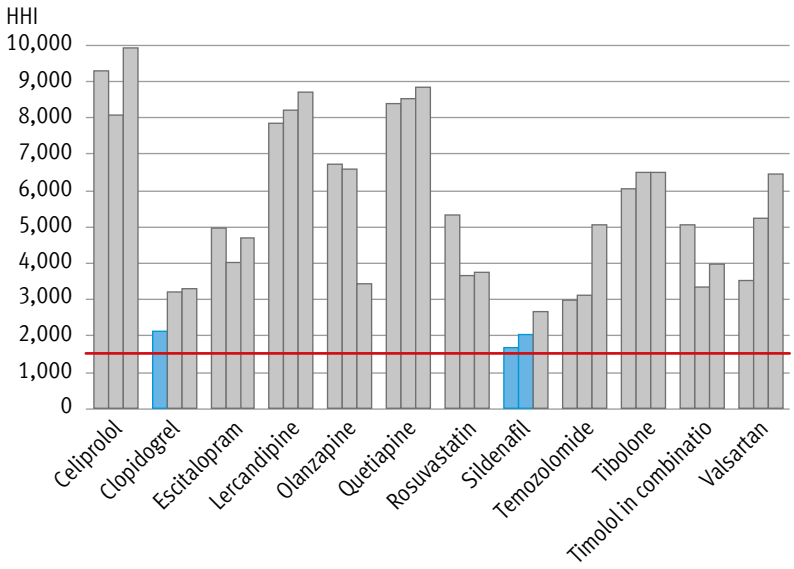
There was a drop in the price index of all of the studied substitution groups after the active substance was included in reference pricing. After the first year, the average price index was 50.7, after the second year 37.9 and after the third year 36.9. After the third year, the lowest price index, 4.6, was observed with olanzapine while also sildenafil and clopidogrel had low price indices, 12.6 and 15.7, respectively. While the price index for olanzapine varied considerably between the three years, the price indices for clopidogrel and sildenafil exhibited constant low levels throughout the three years. Both clopidogrel and sildenafil had high global sales before generic entry, which could explain the active and sustained price decreases. On the other hand, for example, rosuvastatin had higher reimbursed sales in Finland before inclusion in reference pricing than either clopidogrel or sildenafil, and it still showed more restrained price decreases than the other two. One year after being included in reference pricing, the price index for rosuvastatin was 62.5, after two years 52.5 and after three years 47.2. The second year's patent protection issues explain the sharp increase in the price index for olanzapine. However, after the originator brand's patent expired internationally at the end of 2011, two and a half years later than in Finland, more competitors entered the market and price competition started again. (Table 11.)

Table 11. The price index one, two and three years after inclusion in the reference price system.

Active substance	First year	Second year	Third year
Celiprolol	89.6	39.9	23.9
Clopidogrel	16.1	13.1	15.7
Escitalopram	49.0	40.7	38.4
Lercandipine	52.9	51.4	61.8
Olanzapine	35.0	68.8	4.6
Quetiapine	35.8	24.9	28.6
Rosuvastatin	65.2	52.5	47.2
Sildenafil	17.8	9.3	12.6
Temozolamide	49.6	45.7	44.2
Tibolone	63.6	63.6	64.1
Timolol in combination	68.7	60.9	61.4
Valsartan	65.0	44.0	40.2

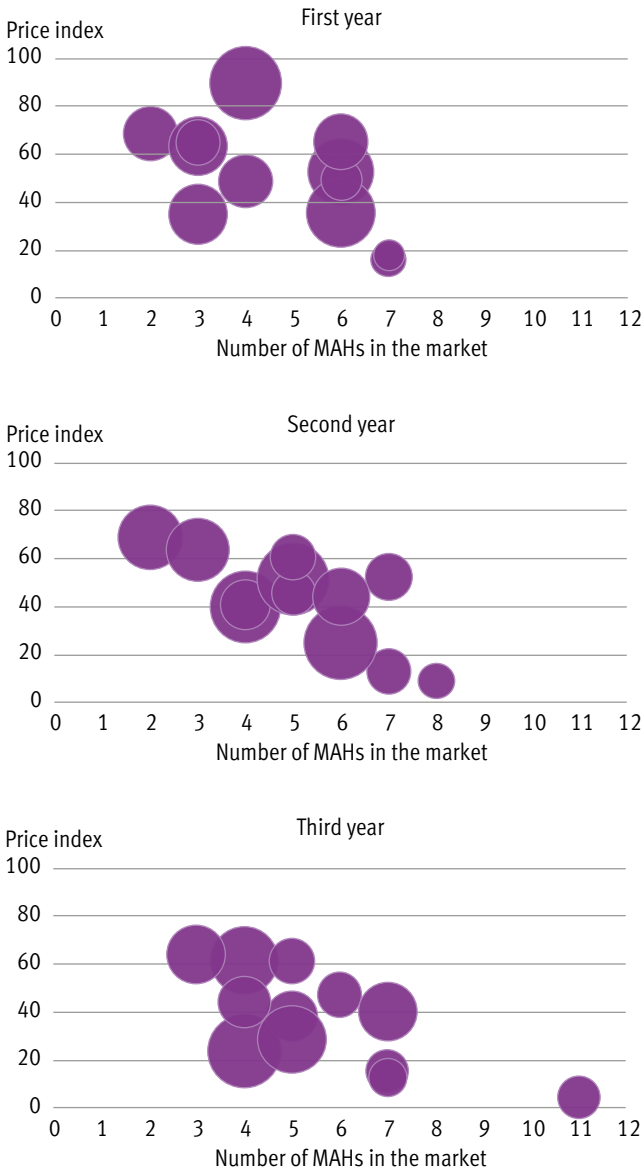
The pharmaceutical markets remained highly concentrated in the reference price system. During the three-year follow-up period, moderately concentrated markets were observed in only two substitution groups, clopidogrel and sildenafil. Besides olanzapine, they were also the substitution groups where the most notable price decreases occurred. The average HHI for the twelve studied active substances was 4,790 for the first year, 5,200 for the second year, and 5,610 for the third year (Figure 7). The market share of the market leader remained very high throughout the three-year follow-up period. In only three out of twelve substitution groups, the market leader had a market share below 40% at some point during the follow-up period. The market share of the market leader ranged between 36% and 97% (mean 67%) during the first year, between 32% and 93% (mean 65%) during the second year, and between 44% and 96% (mean 67%) during the third year. This is despite the fact that the average number of competitors within a substitution group grew from the first year's 4.8 to the second year's 5.2 and finally to the third year's 5.7 (Figure 8, p. 58).

Figure 7. Market concentration according to the Herfindahl-Hirschman Index (HHI) one, two and three years after inclusion in reference pricing[a].



[a] The blue bars indicate moderately concentrated markets (HHI from 1,500 to 2,500). Grey indicates highly concentrated markets (HHI above 2,500). HHI below 1,500 (red line) indicate competitive markets.

Figure 8. Price indices and the number of competitors (marketing authorisation holders, MAHs) in the market after one, two and three years of inclusion in the reference price system[a].



[a] The size of the bubble indicates the level of concentration within the market. The larger the bubble, the higher the concentration.

A regression model was constructed to analyse the impact of different factors on the price development of products included in the reference price system. The actual inclusion in the reference price system had the most notable impact on prices, a drop of almost 30%. In addition, the number of competitors in the market had an impact; each entry of a new generic decreased the price by around 4.5%. At the same time, the dominant position of the market leader and companies' experience of markets under the reference price system had an increasing impact on prices. The later an active substance was included in the reference price system, the higher the price level remained. In other words, each passed quarter increased the price level of a product, once it was included in the reference price system, by 2.9%. (Table 12.)

Table 12. The impact of the factors affecting the price development of products included in the reference price system.

Independent variable	Coefficient	P-value
Constant	87.5088	‹0.0001
Inclusion in the RPS	−29.6126	‹0.0001
Time^2 from inclusion in the RPS	−0.0890	0.0002
Number of competitors	−4.5159	‹0.0001
Dominant position of the market leader	0.1486	0.0158
Copayment rate	−0.1181	0.0600
Companies' experience of the market	2.9349	0.0041

11 Discussion

In the past decades, pharmaceutical expenditures have grown rapidly in Finland. Reasons behind the growth trend vary between drug groups and active substances. This study found that the main reason for the antipsychotic cost growth was the increased use of more expensive treatments while the antidepressant cost growth was mainly due to the increased number of patients treated. Antipsychotic costs continued to grow until the introduction of reference pricing. While the implementation of generic substitution had curbed the antidepressant cost growth for some years, the costs had also taken an upturn again before the implementation of reference pricing. After reference pricing was introduced, both antipsychotic and antidepressant costs were decreased. While the costs have since grown, the total costs were still well below the pre-reference-pricing level in real terms in 2016.

The implementation of the reference price system decreased the daily cost of antipsychotics both in the short term and in the medium-to-long term. The same result applied when other pharmaceutical groups were included in the analysis. However, the size of the impact varied between active substances. Furthermore, the additional impact of reference pricing on previously implemented generic substitution remained low in this study. When analysing the factors associated with prices, this result was affirmed as most of the decreases in prices resulted from the actual inclusion in the reference price system rather than efficient competition. This is due to Finnish pricing regulations that require the maximum wholesale price for generic products to be lower than the on-patent original product's price. During the study years, the required minimum reduction at market entry was 40%. Therefore, much of the observed price decreases result from regulation. Similar results regarding regulation were observed in the UK where a fall in generic prices after a pricing regulation revision in the mid-1990's was deemed to be the result of regulatory action rather than enhanced price competition (Kay and Baines 2000).

However, some competitive effects of the implementation of reference pricing were detected; the number of competitors within a market had a decreasing impact on prices. As the market share of the market leader and the concentration of the market remained very high despite the number of competitors, it appears that the presence of potential competition still had an impact on price competition. In fact, Bergman and Rudholm (2003) found that pharmaceutical prices in Sweden fell in both response to potential (i.e. loss of exclusivity rights) and actual entry of competition. The presence of potential competition lead to a similar reduction, from 4% to 8%, in prices, than the entrance of an additional competitor. (Bergman and Rudholm 2003.)

Generic pharmaceutical markets are highly concentrated in Finland. This is despite the fact that in most cases the number of companies within the market is numerous enough to enable effective competition. In fact, it appears that the number of companies is not the main consideration in Finland but rather the stable position of

the few established companies with substantial market control. Smaller and more aggressively pricing companies did not typically gain a significant market share, if any, even if their product was the only one at or below the reference price. In generic reference pricing, products can be regarded as homogeneous. While some residual brand loyalty exists, the difficulty of smaller companies to access the distribution channel seems to be a contributing factor.

Pharmacies have a significant role in the diffusion of generic products and in steering demand. In systems where the pharmacies' reimbursement is based on the dispensed products' retail price, like in Finland, there is a monetary incentive for pharmacies to dispense higher-priced products (Garattini and Salvioni 1996). Even more importantly, it appears that pharmacies show preference to products from larger, established companies, which makes it difficult for newcomers and smaller companies to gain market share. On the other hand, it has been alleged that the real availability of some products is unreliable. As the real availability of products from the wholesaler is not public information, it is difficult to evaluate this factor. In general, access to wholesalers can also act as a barrier to entry. In Finland, the wholesalers' mark-up is not regulated. However, it can be assumed that larger companies have an advantage over small ones in this sense. Besides company related factors, Finland's geographical location can also act as a barrier to entry or at least diminish the attractiveness of the market to new entrants.

Literature proposes that reference pricing does not provide an incentive for pharmaceutical companies or pharmacies to sell products below the reference price (Danzon and Chao 2000). When examining the price notifications in Finland at the last reference price quarter of 2017, it was observed that about a third of all products subject to the reference price system were priced to their maximum wholesale prices and thus competitive gains were limited. Also, the length of price notification periods may influence companies' willingness to engage in price competition in Finland. While reference prices are set for three-month periods, companies can change their prices every two weeks. This relatively short period allows companies to adopt a watchful waiting type of pricing strategy instead of active price competition.

The impact of health care reforms is typically at its greatest right after implementation, and as time passes, the impact wanes (Altman and Levitt 2002). In this study, it was also observed that as companies gained experience of markets under the reference price system, the impact of the system on prices diminished. The later an active substance was included in the reference price system, the higher the price level remained. Nevertheless, the reference price system brings down the prices of products subject to the system. The effectiveness of the system depends on the implemented system's structure. The grouping of products, the length of reference price periods, and the setting of reference prices are examples of factors that can influence the effectiveness of the system.

A limitation of this study is that the used data has only a limited number of active substances. Therefore, the results should be generalized with caution. While a control group not subject to reference pricing was used in one of the studies, the used methods have limitations in identifying underlying, not reference-price-system related, factors influencing pharmaceutical cost and price development. Furthermore, it is not possible to draw any conclusions on whether the reference price system had any impact on the use of medicines or other health care services.

12 Conclusions

1) The reasons behind rising pharmaceutical expenditures vary between drug groups.
2) The reference price system is associated with decreases in prices in both the short and the medium-to-long term. However, the system is vulnerable to, for example, changes in the number of companies within the market and there is a risk of silent collusion.
3) The additional impact of the reference price system on previously implemented generic substitution is modest, almost non-existent 2.5 years after the implementation. However, the implementation of the reference price system generated immediate level changes in prices and additional short-term savings were achieved.
4) Decreases in the prices of products subject to reference pricing result mainly from regulatory pricing practices, rather than effective competition. Furthermore, companies seem to gain knowledge of markets under the reference price system and adjust their pricing practices; the later a product was included in reference pricing, the lesser the impact of the system on prices was.
5) The generic market sector in Finland is highly concentrated. This held true for each of the first three years of reference pricing observed in this study.

12.1 Policy implications

Based on this study, the following implications for practice can be made:

1) The impact of pharmaceutical reimbursement system reforms, in line with all health care reforms, changes is time. Besides short-term, also long-term evaluations should be made regularly. The ability of the reference price system to influence prices diminishes with time. This means that there is a constant need to revise and fine-tune the implemented measures.
2) While the number of sellers increases after exclusivity rights are lost, there is clearly a chronic problem of too much concentration in the Finnish generic pharmaceutical market. Further consideration is required both to encourage generic entries and to lower the level of concentration in the market.
3) Due to the market dominance of the few large and established companies, they are more able to influence prices than is desirable. This appears to be enforced by pharmacies' stocking and dispensing choices. Besides the currently required information on the actual cheapest product within a reference group, pharmacies' obligation to also have the cheapest products in stock should be considered. This would require the availability of the alternative products from the wholesaler to be transparent. Furthermore, the overall transparency of the pharmaceutical distribution chain should be deliberated, and possible barriers of entry should be lowered if not abolished.
4) Further consideration should also be given to the length of reference price periods and the frequency of price notifications. The timespan between price notifications

is rather short and especially larger, established companies seem to rely on maintaining their market share even if their first price notification of each reference price period is not within the reference price.
5) Further steps to increase the patients' level of information regarding prices should be contemplated. In addition, physicians' price-consciousness in prescribing products where generic alternatives are not on the market should be enhanced.

12.2 Suggestions for further studies

In light of this study and existing literature, the following suggestions are made for future studies:

1) Future research should study the long-term impact of the reference price system on prices and generic market structure. The evaluation should also be extended to include more pharmaceutical groups.
2) The pricing patterns of originator and generic products and subsequent generic entry is an important subject for future research.
3) More research is warranted on the role of pharmacies and wholesalers in price competition on the pharmaceutical market.
4) Future studies should assess whether first mover advantage holds true also in regards to the first generic product entering the market.
5) The impact of the reference price system on the use of pharmaceuticals should be assessed. In addition, the impact on the use of other health care services should be evaluated in order to gain information on the overall impact of the reference price system on health and health care costs.

References

Acts, decrees and government proposals:
395/1987 Medicines Act (Lääkelaki).
1224/2004 Health Insurance Act (Sairausvakuutuslaki).
803/2008 Act on Amending the Medicines Act (Laki lääkelain muuttamisesta).
1101/2016 Act on Amending Sections 57b and 102 of the Medicines Act (Laki lääkelain 57 b ja 102 §:n muuttamisesta).
EU Directive 2001/83/EC. Community code relating to medicinal products for human use.
Government proposal 330/2014.

Aaserud M, Dahlgren AT, Kosters JP, Oxman AD, Ramsay C, Sturm H. Pharmaceutical policies. Effects of reference pricing, other pricing, and purchasing policies. Cochrane Database Syst Rev 2006; (2): CD005979.

Acosta A, Ciapponi A, Aaserud M, et al. Pharmaceutical policies. Effects of reference pricing, other pricing, and purchasing policies. Cochrane Database Syst Rev 2014; (10): CD005979.

Altman DE, Levitt L. The sad history of health care cost containment as told in one chart. Health Aff (Millwood) 2002; Suppl Web Exclusives: W83–84.

Anis AH, Guh DP, Woolcott J. Lowering generic drug prices. Less regulation equals more competition. Med Care 2003; 41 (1): 135–141.

Aronsson T, Bergman MA, Rudholm N. The impact of generic drug competition on brand name market shares. Evidence from micro data. Rev Ind Organ 2001; 19: 425–435.

The Association of Finnish Pharmacies. Annual review 2016. Helsinki: The Association of Finnish Pharmacies, 2017.

Augurzky B, Gohlmann S, Gress S, Wasem J. Effects of the German reference drug program on ex-factory prices of prescription drugs. A panel data approach. Health Econ 2009; 18 (4): 421–436.

Austvoll-Dahlgren A, Aaserud M, Vist G, et al. Pharmaceutical policies. Effects of cap and co-payment on rational drug use. Cochrane Database Syst Rev 2008; (1): CD007017.

Baumgärtel C. Myths, questions, facts about generic drugs in the EU. GaBi Journal 2012; 1 (1): 34–38.

Baumol W. Contestable markets. An uprising in the theory of industry structure. Am Econ Rev 1982; 72 (1): 1–15.

Begg D, Fischer S, Dornbusch R. Market structure and imperfect competition. In: Begg D, Fischer S, Dornbusch R, eds. Economics. Berkshire: McGraw-Hill, 2000a: 149–164.

Begg D, Fischer S, Dornbusch R. Perfect competition and pure monopoly. The limiting cases of market structure. In: Begg D, Fischer S, Dornbusch R, eds. Economics. Berkshire: McGraw-Hill, 2000b: 126–148.

Belloni A, Morgan D, Paris V. Pharmaceutical expenditure and policies. Past trends and future challenges. Paris: OECD, 2016.

Bergman MA, Rudholm N. The relative importance of actual and potential competition. Empirical evidence from the pharmaceuticals market. J Ind Econ 2003; 51 (4): 455–467.

Brekke KR, Holmas TH, Straume OR. Reference pricing, competition, and pharmaceutical expenditures. Theory and evidence from a natural experiment. J Pub Econ 2011; 95: 624–638.

Brekke KR, Königbauer I, Straume OR. Reference pricing of pharmaceuticals. J Health Econ 2007; 26 (3): 613–642.

Buchanan A. Principal/agent relationship and decisionmaking in health care. Bioethics 1988; 2 (4): 317–333.

Caplin A, Nalebuff B. Aggregation and imperfect competition. On the existence of equilibrium. Econometrica 1991; 59: 25–59.

Carrera M, Goldman D, Joyce G, Sood N. Do physicians respond to the costs and cost-sensitivity of their patients. Am Econ J Econ Policy 2018; 10 (1): 113–152.

Chernew ME, Smith DG, Kirking DM, Fendrick AM. Decomposing pharmaceutical cost growth in different types of health plans. Am J Manag Care 2001; 7 (7): 667–673.

Conrad CA. The advantage of being first and competition between firms. Int J Ind Organ 1983; 1 (4): 353–364.

Contoyannis P, Hurley J, Grootendorst P, Jeon SH, Tamblyn R. Estimating the price elasticity of expenditure for prescription drugs in the presence of non-linear price schedules. An illustration from Quebec, Canada. Health Econ 2005; 14 (9): 909–923.

Costa Font J, Rudisill C, Tan S. Brand loyalty, patients and limited generic medicines uptake. Health Policy 2014; 116 (2–3): 224–233.

Danzon PM. Reference pricing. Theory and evidence. In: Lopez-Casasnovas G, Jönsson B, eds. Reference pricing and pharmaceutical policy. Perspectives on economics and innovation. New York, NY: Springer, 2001: 86–126.

Danzon PM, Chao LW. Does regulation drive out competition in pharmaceutical markets? J Law Econ 2000; 43 (2): 311–357.

Danzon PM, Ketcham JD. Reference pricing of pharmaceuticals for Medicare. Evidence from Germany, the Netherlands, and New Zealand. Front Health Policy Res 2004; 7: 1–54.

Danzon PM, Pauly MV. Health insurance and the growth in pharmaceutical expenditure. J Law Econ 2002; 45 (S2): 587–613.

Darby MR, Karni E. Free competition and the optimal amount of fraud. J Law Econ 1973; 16 (1): 67–88.

de Joncheere K, Haaijer-Ruskamp FM, Rietveld AH, Dukes MNG. Scope of the problem. In: Dukes MNG, Haaijer-Rustkamp FM, de Jonchere CP, Rietveld AH, eds. Drugs and money. Prices, affordability and cost containment. Amsterdam: IOS Press, 2002: 7–13.

de Meijer C, Wouterse B, Polder J, Koopmanschap M. The effect of population aging on health expenditure growth. A critical review. Eur J Ageing 2013; 10 (4): 353–361.

Dixit A. Recent developments in oligopoly theory. The American Economic Review 1982; 72 (2): 12–17.

Dubey R, Dubey J. Pharmaceutical product differentiation. A strategy for strengthening product pipeline and life cycle management. J Med Mark 2009; 9 (2): 104–118.

Dukes M, Haaijer-Ruskamp FM, de Jonchere C, Rietveld AH, eds. Drugs and money. Prices, affordability and cost containment. Amsterdam: World Health Organization, 2003.

Dulleck U, Kerschbamer R. On doctors, mechanics and computer specialists. The economics of credence goods. Journal of Economic Literature 2006; 44 (1): 5–42.

Dylst P, Simoens S. Does the market share of generic medicines influence the price level? A European analysis. Pharmacoeconomics 2011; 29 (10): 875–882.

Dylst P, Vulto A, Simoens S. The impact of reference-pricing systems in Europe. A literature review and case studies. Expert Rev Pharmacoecon Outcomes Res 2011; 11 (6): 729–737.

Ess SM, Schneeweiss S, Szucs TD. European healthcare policies for controlling drug expenditure. Pharmacoeconomics 2003; 21 (2): 89–103.

European Commission. Competition. Antitrust procedures in abuse of dominance. Article 102 TFEU cases. Brussels: European Commission, 2013.

European Commission. Patent protection in the EU. Brussels: European Commission, 2018. Available at: ‹https://ec.europa.eu/growth/industry/intellectual-property/patents_en›. Accessed 21 Jan 2018.

EFPIA. The pharmaceutical industry in figures. Brussels: EFPIA, 2015.

EFPIA. The pharmaceutical industry in figures. Key data 2017. Brussels: EFPIA, 2017.

European Medicines Agency. Questions and answers on generic medicines. London: European Medicines Agency, 2012. Available at: ‹http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/11/WC500012382.pdf›. Accessed 12 Oct 2017.

Fimea and Kela. Finnish statistics on medicines. Helsinki: Fimea and Kela, 1994–2016.

Fimea and Kela. Finnish statistics on medicines 2015. Helsinki: Fimea and Kela, 2016.

Fimea and Kela. Clinical drug trials. In: Fimea and Kela. Finnish Statistics on medicines 2016. Helsinki: Fimea and Kela, 2017a: 54–55.

Fimea and Kela. Finnish statistics on medicines 2016. Helsinki: Fimea and Kela, 2017b.

Fiorito R, Kollintzas T. Public goods, merit goods, and the relation between private and government consumption. Eur Econ Rev 2004; 48 (6): 1367–1398.

Galizzi MM, Ghislandi S, Miraldo M. Effects of reference pricing in pharmaceutical markets. A review. Pharmacoeconomics 2011; 29 (1): 17–33.

Garattini L, Salvioni F. Distribution margins. A European overview. Pharm Pricing Rev 1996; 1 (8): 154–157.

Garattini L, Tediosi F. A comparative analysis of generics markets in five European countries. Health Policy 2000; 51 (3): 149–162.

Gerdtham UG, Lundin D. Why did drug spending increase during the 1990s? A decomposition based on Swedish data. Pharmacoeconomics 2004; 22 (1): 29–42.

Ghislandi S, Armeni P, Jommi C. The impact of generic reference pricing in Italy, a decade on. Eur J Health Econ 2013; 14 (6): 959–969.

Glowicka E, Lorincz S, Pesaresi E, Romero LS, Verouden V. Generic entry in prescription medicines in the EU. Main characteristics, determinants and effects. Brussels: European Commission, 2009.

Goldman DP, Joyce GF, Zheng Y. Prescription drug cost sharing. Associations with medication and medical utilization and spending and health. JAMA 2007; 298 (1): 61–69.

Grootendorst P, Stewart D. A re-examination of the impact of reference pricing on anti-hypertensive drug plan expenditures in British Columbia. Health Econ 2006; 15 (7): 735–742.

Grootendorst PV, Dolovich LR, O'Brien BJ, Holbrook AM, Levy AR. Impact of reference-based pricing of nitrates on the use and costs of anti-anginal drugs. CMAJ 2001; 165 (8): 1011–1019.

Grootendorst PV, Dolovich LR, Holbrook AM, Levy AR, O'Brien BJ. The impact of reference pricing of cardiovascular drugs on health care costs and health outcomes. Evidence from British Columbia. Volume II. Technical report. Hamilton: Research Institute for Quantitative Studies in Economics and Population, 2002.

Grootendorst PV, Marshall JK, Holbrook AM, Dolovich LR, O'Brien BJ, Levy AR. The impact of reference pricing of nonsteroidal anti-inflammatory agents on the use and costs of analgesic drugs. Health Serv Res 2005; 40 (5 Pt 1): 1297–1317.

Hassali MA, Shafie AA, Jamshed S, Ibrahim MI, Awaisu A. Consumers' views on generic medicines. A review of the literature. Int J Pharm Pract 2009; 17 (2): 79–88.

Haula T, Koskinen H, Valtonen H. Viitehintajärjestelmä ja asiakkaiden vaihtokiellot. Dosis 2014; 30 (4): 257–263.

Hollis A. The importance of being first. Evidence from Canadian generic pharmaceuticals. Health Econ 2002; 11 (8): 723–734.

Hotelling H. Stability in competition. Econ J 1929; 39 (153): 41–57.

IMS Health. Global spending on medicines in 2020. Outlook and implications. Danbury, CT: IMS Health, 2015. Available at: https://www.iqvia.com/-/media/iqvia/pdfs/institute-reports/global-medicines-use-in-2020.pdf?la=uk-ua&hash=968B71C0B0769A179F3A56E331C62754EEF74752›. Accessed 27 Apr 2018.

Kaiser U, Mendez SJ. How do drug prices respond to a change from external to internal reference pricing? Evidence from Danish regulatory reform. Mannheim: ZEW, Discussion Paper 15-004, 2015.

Kaiser U, Mendez SJ, Ronde T, Ullrich H. Regulation of pharmaceutical prices. Evidence from a reference price reform in Denmark. Bonn: IZA, Discussion Paper 7248, 2013.

Kaiser U, Mendez SJ, Ronde T, Ullrich H. Regulation of pharmaceutical prices. Evidence from a reference price reform in Denmark. J Health Econ 2014; 36: 174–187.

Kanavos P, Costa-Font J, Seeley E. Competition in off-patent drug markets. Issues, regulation and advice. Econ Policy 2008; 23 (55): 500–544.

Kanavos P, Schurer W, Vogler S. The pharmaceutical distribution chain in the European Union. Structure and impact on pharmaceutical prices. Brussels: European Commission, 2011.

Karampli E, Souliotis K, Polyzos N, Kyriopoulos J, Chatzaki E. Pharmaceutical innovation. Impact on expenditure and outcomes and subsequent challenges for pharmaceutical policy, with a special reference to Greece. Hippokratia 2014; 18 (2): 100–106.

Kay A, Baines D. The rapid increase in generic prices in the UK. A failure of competition or regulation. Public Money Manage 2000; 20 (3): 35–38.

Kela. Generic substitution and the reference price system. Helsinki: Kela, 2017a. Available at: ‹http://www.kela.fi/web/en/generic-substitution-and-the-reference-price-system›. Accessed 21 Oct 2017.

Kela. Statistical database Kelasto. Helsinki: Kela, 2017b. Available at: ‹http://raportit.kela.fi/ibi_apps/WFServlet?IBIF_ex=NIT127AL›. Accessed 11 Oct 2017.

Kela. Reimbursements for medicine expenses. Helsinki: Kela, 2017c. Available at: ‹http://www.kela.fi/web/en/medicine-expenses›. Accessed 12 Oct 2017.

Kesselheim AS, Misono AS, Lee JL, et al. Clinical equivalence of generic and brand-name drugs used in cardiovascular disease. A systematic review and meta-analysis. JAMA 2008; 300 (21): 2514–2526.

Kibicho J, Pinkerton SD. Multiple drug cost containment policies in Michigan's Medicaid program saved money overall, although some increased costs. Health Aff (Millwood) 2012; 31 (4): 816–826.

Kildemoes HW, Christiansen T, Gyrd-Hansen D, Kristiansen IS, Andersen M. The impact of population ageing on future Danish drug expenditure. Health Policy 2006; 75 (3): 298–311.

Koskinen H, Martikainen JE, Maljanen T, Ahola E, Saastamoinen LK. Viitehintajärjestelmän vaikutus järjestelmään kuuluvien ja sen ulkopuolella olevien lääkkeiden kustannuksiin. In: Klavus J, ed. Terveystaloustiede 2013. Helsinki: THL, 2013: 28–31.

Koskinen H, Ahola E, Saastamoinen LK, Mikkola H, Martikainen JE. The impact of reference pricing and extension of generic substitution on the daily cost of antipsychotic medication in Finland. Health Econ Rev 2014; 4 (9).

Koskinen H, Mikkola H, Saastamoinen LK, Ahola E, Martikainen JE. Time series analysis on the impact of generic substitution and reference pricing on antipsychotic costs in Finland. Value Health 2015; 18 (8): 1105–1112.

Kyle MK. Pharmaceutical price controls and entry strategies. Rev Econ Stat 2007; 89 (1): 88–99.

LaFleur J, Fish L, Brixner DI. Trends in pharmaceutical expenditures. The impact on drug benefit design. Am Health Drug Benefits 2008; 1 (4): 29–34.

Leopold C, Mantel-Teeuwisse AK, Vogler S, et al. Effect of the economic recession on pharmaceutical policy and medicine sales in eight European countries. Bull World Health Organ 2014; 92 (9): 630–640D.

Manning WG, Newhouse JP, Duan N, Keeler EB, Leibowitz A, Marquis MS. Health insurance and the demand for medical care. Evidence from a randomized experiment. Am Econ Rev 1987; 77 (3): 251–277.

Marshall JK, Grootendorst PV, O'Brien BJ, Dolovich LR, Holbrook AM, Levy AR. Impact of reference-based pricing for histamine-2 receptor antagonists and restricted access for proton pump inhibitors in British Columbia. CMAJ 2002; 166 (13): 1655–1662.

Martikainen JE, Kiviniemi V, Oravalahti T, Enlund H, Happonen P. Lääkkeen vaihdon kieltäminen aiheuttaa merkittäviä kustannuksia. Lääkärilehti 2016; 71 (21): 1544–1546.

Ministry of Social Affairs and Health in Collaboration with the World Health Organization. Finland Pharmaceutical Country Profile. Helsinki: Ministry of Social Affairs and Health, 2011.

Miraldo M. Reference pricing and firms' pricing strategies. J Health Econ 2009; 28 (1): 176–197.

Moreno-Torres I. Generic drugs in Spain. Price competition vs. moral hazard. Barcelona: XREAP, Working papers 4, 2011.

Moreno-Torres I, Puig-Junoy J, Raya JM. The impact of repeated cost containment policies on pharmaceutical expenditure. Experience in Spain. Eur J Health Econ 2011; 12 (6): 563–573.

Morgan SG. Booming prescription drug expenditure. A population-based analysis of age dynamics. Med Care 2005; 43 (10): 996–1008.

Mossialos E, Walley T, Mrazek M. Regulating pharmaceuticals in Europe. An overview. In: Mossialos E, Walley T, Mrazek M, eds. Regulating pharmaceuticals in Europe. Striving for efficiency, equityand quality. European Observatory on Health Systems and Policies. Berkshire: Open University Press, 2004: 1–37.

Mrazek M, Mossialos E. Regulating pharmaceutical prices in the European Union. In: Mossialos E, Mrazek E, Walley T, eds. Regulating pharmaceuticals in Europe. Striving for efficiency, equity and quality. Berkshire: Open University Press, 2004: 114–129.

Nyman JA. The economics of moral hazard revisited. J Health Econ 1999; 18 (6): 811–824.

OECD. Pharmaceutical pricing policies in a global market. Paris: OECD, 2008.

OECD. Generic pharmaceuticals. Note by Finland. Paris: OECD, 2014.

OECD. Research and development in the pharmaceutical sector. Health at a glance 2015. OECD Indicators. Paris: OECD, 2015.

OECD. Focus on health spending. Expenditures by disease, age and gender. Paris: OECD, 2016a.

OECD. Health at a glance. Europe 2016. State of health in the EU cycle. Paris: OECD, 2016b.

OECD. Pharmaceutical spending (indicator). Paris: OECD, 2017. Available at: ‹http://dx.doi.org/10.1787/998febf6-en›. Accessed 31 Jan 2017.

Panteli D, Arickx F, Cleemput I, et al. Health systems in transition. Pharmaceutical regulation in 15 European countries. Review. Copenhagen: European Observatory on Health Systems and Policies, 2016.

Pauwels K, Huys I, Vogler S, Casteels M, Simoens S. Managed entry agreements for oncology drugs. Lessons from the European experience to inform the future. Front Pharmacol 2017; 8: 171.

Pavcnik N. Do pharmaceutical prices respond to insurance? Cambridge, MA: National Bureau of Economics, Working Paper 7865, 2000.

Pavenik N. Do pharmaceutical prices respond to potential patient out-of-pocket expenses? Rand J Econ 2002; 33 (3): 469–487.

Pelkonen L. Medicines reimbursement system in Finland. Sic! 2011; 1 (2): 10–13.

Pharmaceuticals Pricing Board. Decision of the Pharmaceuticals Pricing Board authorizing the Director of the Board to decide on matters concerning the reference price system and the reimbursement status and price of a medicinal product. Helsinki: Pharmaceuticals Pricing Board, 2015. Available at: ‹http://www.hila.fi/en/operations-and-organisation/legislation›. Accessed 11 Oct 2017.

Pharmaceuticals Pricing Board. Reduction of maximum wholesale price. Helsinki: Pharmaceuticals Pricing Board, 2016. Available at: ‹http://www.hila.fi/275›. Accessed 31 Oct 2017.

Pharmaceuticals Pricing Board. Reference price group. Parallel-imported and parallel-distributed product. Helsinki: Pharmaceuticals Pricing Board, 2017. Available at: ‹http://www.hila.fi/286›. Accessed 31 Oct 2017.

Porter ME. How competitive forces shape strategy. Harvard Bus Rev 1979; 57 (2): 137–145.

Porter ME. Competitive strategy. Techniques for analyzing industries and competitors. New York, NY: Free press, 1980: 7–17.

Puig-Junoy J. The impact of generic reference pricing interventions in the statin market. Health Policy 2007; 84 (1): 14–29.

Puig-Junoy J. Price regulation systems in the pharmaceutical market. In: Puig-Junoy J, ed. The public financing of pharmaceuticals. An economic approach. Cheltenham: Elgar, 2005: 35–58.

Remuzat C, Urbinati D, Mzoughi O, El Hammi E, Belgaied W, Toumi M. Overview of external reference pricing systems in Europe. J Mark Access Health Policy 2015; 3. Doi: 10.3402/jmahp.v3.27675.

Rice T. The desirability of market-based health reforms. A reconsideration of economic theory. In: Barer ML, Getzen TE, Stoddart GL, eds. Health, health care and health economics. Perspectives on distribution. Chichester: Wiley, 1998: 415–464.

Rietveld AH, Haaijer-Ruskamp FM. Policy options for cost containment of pharmaceuticals. Int J Risk Saf Med 2002; 15: 29–54.

Ruggeri K, Nolte E. Pharmaceutical pricing. The use of external reference pricing. Rand Health Q 2013; 3 (2): 6.

Saastamoinen LK, Martikainen JE, Haula T. The first year of reference pricing. In: Fimea and Kela. Finnish statistics on medicines 2009. Helsinki: Fimea and Kela, 2010: 45–50.

Sawyer DO. Pharmaceutical reimbursement and drug cost control. The MAC experience in Maryland. Inquiry 1983; 20 (1): 76–87.

Schmalensee R. Product differentiation advantages of pioneering brands. The American Economic Review 1982; 72 (3): 349–365.

Schneeweiss S, Maclure M, Soumerai SB. Prescription duration after drug copay changes in older people. Methodological aspects. J Am Geriatr Soc 2002a; 50 (3): 521–525.

Schneeweiss S, Soumerai SB, Glynn RJ, Maclure M, Dormuth C, Walker AM. Impact of reference-based pricing for angiotensin-converting enzyme inhibitors on drug utilization. CMAJ 2002b; 166 (6): 737–745.

Schneeweiss S, Walker AM, Glynn RJ, Maclure M, Dormuth C, Soumerai SB. Outcomes of reference pricing for angiotensin-converting-enzyme inhibitors. N Engl J Med 2002c; 346 (11): 822–829.

Schneeweiss S, Soumerai SB, Maclure M, Dormuth C, Walker AM, Glynn RJ. Clinical and economic consequences of reference pricing for dihydropyridine calcium channel blockers. Clin Pharmacol Ther 2003; 74 (4): 388–400.

Scott Morton FM. Entry decisions in the generic pharmaceutical industry. Rand J Econ 1999; 30 (3): 421–440.

Scott Morton FM, Kyle MK. Markets for pharmaceutical products. In: Pauly MV, McGuire TG, Barros PP, eds. Handbook of health economics. Volume 2. Oxford: Elsevier, 2012: 763–824.

Selten R. A simple model of imperfect competition, where 4 are few and 6 are many. International Journal of Game Theory 1973; 2 (1): 141–201.

Serra-Sastre V, McGuire A. Diffusion of health technologies. Evidence from the pharmaceutical sector. In: Costa-Font J, Courbage C, McGuire A, eds. The economics of new technologies. Incentives, organization, and financing. Oxford: Oxford University Press, 2009: 53–74.

Shaked A, Sutton J. Relaxing price competition through product differentiation. Rev Econ Stud 1982; XLIX: 3–13.

Shaked A, Sutton J. Product differentiation and industrial structure. J Ind Econ 1987; 36 (2): 131–146.

Shepherd WG. Dim prospects. Effective competition in telecommunications, railroads and electricity. Antitrust Bull Spring 1997; 42 (1): 151–175.

Shireman TI, Rigler SK, Jachna CM, Griebling TL, Eng ML. The cost effect of newer medication adoption in an older Medicaid cohort. J Am Geriatr Soc 2005; 53 (8): 1366–1373.

Silberston A. Economies of scale in theory and practice. Econ J 1972; 82 (325): 369–391.

Simonsen M, Skipper L, Skipper N. Price sensitivity of demand for prescription drugs. Exploiting a regression kink design. J Appl Econom 2016; 31 (2): 320–337.

Singh N, Vives X. Price and quantity competition in a differentiated duopoly. Rand J Econom 1984; 15 (4): 546–554.

Smith A. An inquiry into the nature and causes of the wealth of nations. London: Strahan and Cadell, 1776.

Sorenson C, Drummond M, Bhuiyan Khan B. Medical technology as a key driver of rising health expenditure. Disentangling the relationship. Clinicoecon Outcomes Res 2013; 5: 223–234.

Stargardt T. The impact of reference pricing on switching behaviour and healthcare utilisation. The case of statins in Germany. Eur J Health Econ 2009. Doi: 10.1007/s10198-009-0172-3.

US Department of Justice. 5.3 Market concentration. Washington, DC: US Department of Justice, 2015. Available at: ‹https://www.justice.gov/atr/horizontal-merger-guidelines-08192010›. Accessed 22 Oct 2015.

US Department of Justice and the Federal Trade Commission. Horizontal merger guidelines. Washington, DC: The US Department of Justice and the Federal Trade Commission, 2010. Available at: ‹http://www.justice.gov/atr/public/guidelines/hmg-2010.html›. Accessed 29 June 2015.

Valliluoto S. Lääkehuollosta lääkemarkkinoihin. Arvoketju ja säätely. Helsinki: Kilpailuvirasto, 2012.

Wagner AK, Soumerai SB, Zhang F, Ross-Degnan D. Segmented regression analysis of interrupted time series studies in medication use research. J Clin Pharm Ther 2002; 27 (4): 299–309.

WHO. Public-private roles in the pharmaceutical sector. Implications for equitable access and rational drug use. Geneva: WHO, 1997. Available at: ‹http://apps.who.int/medicinedocs/en/d/Jwhozip27e/6.3.html#Jwhozip27e.6.3›. Accessed 9 Oct 2017.

WHO. Pharmaceutical industry. Geneva: WHO, 2005. Available at: ‹http://web.archive.org/web/20050429113651/http:/www.who.int/trade/glossary/story073/en/›. Accessed 6 Oct 2017.

WHO. Economics for pharmaceutical management. Paris: WHO, 2012.

WHO. 9.7 Annex G Evidence summary 3. Application of cost-plus pricing formulae for pharmaceutical products. In: WHO, ed. WHO Guideline on country pharmaceutical pricing policies. Geneva: WHO, 2015: 73–76.

WHO Collaborating Centre for Drug Statistics Methodolgy. ATC/DDD Index 2018. Oslo: WHO Collaborating Centre for Drug Statistics Methodolgy, 2018. Available at: ‹http://www.whocc.no/atc_ddd_index/›. Accessed 30 Dec 2017.

WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies. Glossary. Preferred terms. Vienna: WHO Collaborating Centre for pharmaceutical pricing and reimbursement policies, 2016. Available at: ‹http://whocc.goeg.at/Glossary/PreferredTerms›. Accessed 12 Oct 2017.

WHO Collaborating Centre for Pharmaceutical Pricing and Reimbursement Policies. Preferred terms glossary. Vienna: WHO Collaborating Centre for pharmaceutical pricing and reimbursement policies, 2017. Available at: ‹http://whocc.goeg.at/Glossary/PreferredTerms›. Accessed 8 Oct 2017.

Zhang F, Wagner AK, Soumerai SB, Ross-Degnan D. Methods for estimating confidence intervals in interrupted time series analyses of health interventions. J Clin Epidemiol 2009; 62 (2): 143–148.

Appendix

Literature search strategy.

Database Date of search	Platform or vendor	Search profiles	Results
Cochrane Database of Systematic Reviews (CDSR) Database of Abstracts of Reviews of Effects (DARE) Cochrane Central Register of Controlled Trials (CENTRAL) Cochrane Methodology Register (CMR) Health Technology Assessment Database (HTA) NHS Economic Evaluation Database (NHSEED) 10 Feb 2017	The Cochrane Library	1 “reference pricing” or “reference price system” or “reference price systems”:ti,ab,kw 2 prices:ti,ab,kw or costs:ti,ab,kw 1 AND 2 Publication Year from 2011 to 2017	8 (of which 1 CDSR, 1 DARE and 6 CENTRAL)
PubMed 2 Oct 2017	National Library of Medicine, USA	1 ((reference pricing[Text Word]) OR reference price system[Text Word]) OR reference price systems[Text Word] 2 (prices[Title/Abstract]) OR costs[Title/Abstract] 3 ((“english”[Language]) OR “finnish”[Language]) OR “swedish”[Language] 4 1 AND 2 AND 3 AND (“2011”[Date - Publication] : “3000”[Date - Publication])	55
EMBASE 2 Oct 2017	Elsevier	1 ‘reference pricing’ OR ‘reference price system’ OR ‘reference price systems’ 2 prices:ab,ti OR costs:ab,ti 3 1 AND 2 AND AND [embase]/lim NOT [medline]/lim AND ([english]/lim OR [finnish]/lim OR [swedish]/lim) AND [2011-2017]/py	136
EconLit 2 Oct 2017	ProQuest	1 (“reference pricing” OR “reference price system” OR “reference price systems”) AND prices 2 (ti(prices) OR ti(costs) OR ab(prices) OR ab(costs)) 3 1 AND 2 AND Publication date: 2011 - 2017	17
PAIS Index 2 Oct 2017	ProQuest	1 “reference pricing” OR “reference price system” OR “reference price systems” 2 (ti(prices) OR ab(costs) OR ti(prices) OR ab(costs)) 3 1 AND 2 Publication date: 2011–2017	7
Sociological Abstracts 2 Oct 2017	ProQuest	1 “reference pricing” OR “reference price system” OR “reference price systems” 2 (ti(prices) OR ab(costs) OR ti(prices) OR ab(costs)) 3 1 AND 2 Publication date: 2011–2017	1
Results: 224 references altogether, after removing duplicates: 183			

RECENT PUBLICATIONS IN THE STUDIES IN SOCIAL SECURITY AND HEALTH SERIES

149 **Tervola J.** Supporting gender equality and integration. Immigrant families' child care choices in the Nordic policy context. 2018. ISBN 978-952-284-035-6 (print), 978-952-284-036-3 (pdf).

148 **Pekola P.**The effects of competition and regulation on quality in physiotherapy. 2018. ISBN 978-952-284-033-2 (print), 978-952-284-034-9 (pdf).

147 **Romakkaniemi M, Lindh J, Laitinen M.** Nuorten aikuisten osallisuus ja sosiaalinen kuntoutus Lapissa. 2018. ISBN 978-952-284-031-8 (nid.), ISBN 978-952-284-032-5 (pdf).

146 **Aaltonen K.** Affordability of medicines from the pharmaceutical system perspective. Comparative analysis of Finland and New Zealand. 2017. ISBN 978-952-284-019-6 (print), 978-952-284-020-2 (pdf).

145 **Rintala A, Hakala S, Sjögren T, toim.** Etäteknologian vaikuttavuus liikunnallisessa kuntoutuksessa. Järjestelmällinen kirjallisuuskatsaus ja meta-analyysi. 2017. ISBN 978-952-284-017-2 (nid.), 978-952-284-018-9 (pdf).

144 **Harkko J, Lehikoinen T, Lehto S, Ala-Kauhaluoma M** Onko osa nuorista vaarassa syrjäytyä pysyvästi? Nuorten syrjäytymisriskit ja aikuisuuteen siirtymistä tukeva palvelujärjestelmä. 2016. ISBN 978-952-284-009-7 (nid.), 978-952-284-010-3 (pdf).

143 **Pitkänen T, Holopainen A, Jokela K, Kaskela T, Levola J, Tourunen J.** Aivotoiminnan häiriöiden yhteydessä yleisesti koetut psykososiaaliset vaikeudet. PARADISE24-kyselyn tutkimusperusta. 2016. ISBN 978-952-284-007-3 (nid.), ISBN 978-952-284-008-0 (pdf).

142 **Merikoski M, Enlund H.** Biologisten lääkkeiden käyttöönotto ja käyttö Suomessa. Terveydenhuollon käytäntöjä ja näkökulmia. 2016. ISBN 978-951-669-997-7 (nid.), ISBN 978-951-669-998-4 (pdf).

141 **Seppänen-Järvelä R, Syrjä V, Juvonen-Posti P, Pesonen S, Laaksonen M, Tuusa M, Savinainen M, Henriksson M.** Yhteistoimintaa ja yksilöllisiä valintoja kuntoutumisen polulla. Kelan työhönkuntoutuksen kehittämishankkeen tapaustutkimus. 2015. ISBN 978-951-669-991-5 (nid.), ISBN 978-951-669-992-2 (pdf).

Pharmaceutical prices and expenditures are discussed increasingly around the world. Different mechanisms, such as promoting competition, have been contemplated in an attempt to contain costs. In this, reference price systems have been a widely used method.

This study aims to examine the impact of a generic reference price system on prices, market structure and competition, with a special focus on antipsychotics. Furthermore, the additional impact of reference pricing over and above the impact of previously implemented generic substitution is investigated.

While price decreases were obtained, most of them resulted from pharmaceutical pricing regulations rather than effective competition. The generic market sector appears highly concentrated. Furthermore, the additional impact of reference pricing on previously implemented generic substitution remains modest.

The Social Insurance Institution of Finland
Kela Research
Phone +358 20 634 11
julkaisut@kela.fi
www.kela.fi/research
www.kela.fi/tutkimus
www.fpa.fi/forskning

ISBN 978-952-284-039-4 (print)
ISBN 978-952-284-040-0 (pdf)
ISSN-L 1238-5050
ISSN 1238-5050 (print)
ISSN 2323-7724 (pdf)